FOR MORE INFORMATION

Emory University School of Medicine
Department of Medicine
Division of Infectious Diseases
49 Jesse Hill Jr. Drive, Atlanta, Georgia, 30303
Email: **tb@emory.edu**

Georgia Department of Public Health
Division of Health Protection
2 Peachtree Street, NW, Atlanta, Georgia 30303
404-657-2634
https://dph.georgia.gov/tuberculosis-tb-prevention-and-control

TB Hotline for Physicians
1-800-4TB-DOCS (1-800-482-3627)

CDC Division of TB Elimination Web Page
http://www.cdc.gov/tb/

For additional copies of this guide, call:
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EMORY UNIVERSITY SCHOOL OF MEDICINE

DPH Georgia Department of Public Health

Georgia Tuberculosis Reference Guide

2014

January 2014

Dear Clinician,

This booklet responds to clinicians' questions about tuberculosis infection, disease, and control. The standards and guidelines are based on the work and experience of the American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA), Emory University, the World Health Organization (WHO), and the Atlanta TB Prevention Coalition. This edition contains updated recommendations on the treatment of latent tuberculosis infection (LTBI) and treatment of active tuberculosis disease.

The treatment of a patient with TB always requires a clinician to exercise clinical and professional judgment. These guidelines provide a framework for the treatment of patients with TB infection or disease. Standardized treatment offers the greatest opportunity for controlling tuberculosis.

This is not an exhaustive treatment of the subjects covered. It is an accessible reference guide. Since guidelines for treating and controlling TB continue to evolve, it is appropriate for clinicians to check further for new treatment regimens.

Detailed information is available from:

- Your county public health department and the Georgia Department of Public Health, Tuberculosis Control Program: 404-657-2634

Sincerely,

Henry M. Blumberg, M.D.
Emory University School of Medicine

Susan M. Ray, M.D.
Emory University School of Medicine

Acknowledgements

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Abbreviations

AFB: Acid-Fast Bacilli
AIDS: Acquired Immunodeficiency Syndrome
ART: Antiretroviral Therapy
AST: Antimicrobial Susceptibility Testing
BCG: Bacillus Calmette-Guerin
BID: Bis in die (Twice Daily)
CAP: Capreomycin
CBC: Complete Blood Count
CNS: Central Nervous System
CXR: Chest X-Ray
DHT: Delayed-type Hypersensitivity
DOPT: Directly Observed Preventive Therapy
DOT: Directly Observed Therapy
EMB: Ethambutol
FQN: Fluoroquinolone
HAART: Highly Active Antiretroviral Therapy
HCV: Hepatitis C Virus
HIV: Human Immunodeficiency Virus
IM: Intramuscular
INH: Isoniazid
IV: Intravenous
KM: Kanamycin
LFT: Liver Function Test
LTBI: Latent Tuberculosis Infection
MDR: Multidrug Resistant
NRTI: Nucleoside Reverse Transcriptase Inhibitor

NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor
PAS: Para-aminosalicylic Acid
PI: Protease Inhibitor
PO: *Per os* (Oral)
PPD: Purified Protein Derivative
PZA: Pyrazinamide
RFB: Rifabutin
RIF: Rifampin
RPT: Rifapentine
SM: Streptomycin
TB: Tuberculosis
TST: Tuberculin Skin Test
TU: Tuberculin Unit
XDR: Extensively Drug-resistant

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I. Classification System for Tuberculosis

Class O: ***No TB Exposure—Not Infected***

No history of exposure. Negative reaction to the tuberculin skin test.

Class I: ***TB Exposure—No Evidence of Infection***

History of exposure (contact to a case of TB) and negative reaction to the tuberculin skin test.

Class II: ***TB Infection—No Disease***

Positive reaction to the tuberculin skin test, no clinical or radiographic evidence of TB, and/or negative bacteriologic studies (if done).

Class III: ***Current TB Disease***

Clinical, bacteriological, and/or radiographic evidence of current tuberculosis. This is established most definitively by isolation of *M. tuberculosis*.

Class IV: ***Previous TB Disease***

History of episode(s) of TB, or abnormal but stable radiographicfindings, positive reaction to the tuberculin skin test, negative bacteriologic studies (if done) and no clinical or radiographic evidence of current disease.

Class V: ***TB Suspected***

Diagnosis pending. Patient should not remain in this category for more than three months.

II. Epidemiology

- Worldwide**,** TB is an enormous global public health problem. The World Health Organization (WHO) estimates that there were 8.7 million new cases of TB disease and more than 1.4 million deaths due to TB in 2012.

- TB is the second leading cause of death due to an infectious disease (after HIV/AIDS). TB is also the leading cause of death in persons with HIV/AIDS worldwide (although not in the United States).

- One-third of the world's population is infected with and harbors *Mycobacterium tuberculosis* (i.e., latent TB infection) and therefore is at risk for developing active disease.

- The interaction between the TB epidemic and the HIV/AIDS epidemic is lethal. TB adds to the burden of illness of HIV-infected people and shortens their life expectancy, while the HIV epidemic spurs the spread of TB.

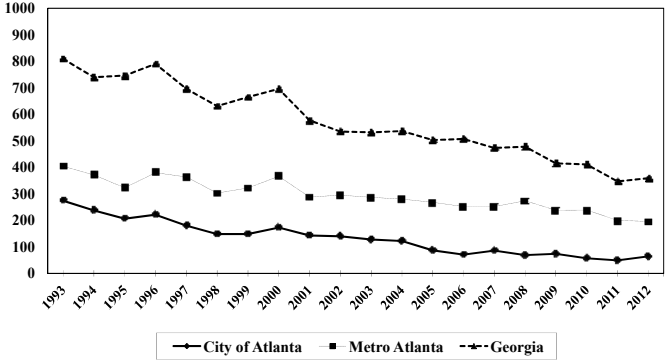
- In the **U.S.** there was a resurgence of TB from 1985 to 1992. The number of cases increased 20% during this time period, peaking in 1992 with 26,673 cases reported. The increased case numbers were attributed to the HIV epidemic, decreased funding for public health, immigration from countries where TB is endemic, and transmission of TB in congregate settings such as hospitals, correctional institutions and homeless shelters.

- Due to a number of public health interventions, TB cases began declining in 1992 in the U.S. From 1992 through 2012, there has been a 61% decrease in the number of cases, as TB control was strengthened nationally. In 2012, the U.S. reported 9,951 new TB cases (3.2 per 100,000 population). The decrease is attributed to strengthened public health infrastructure for TB prevention and control nationwide. Concern is rising about a new wave of complacency in TB control. In recent years, federal TB control funding has decreased when adjusted for inflation.

- TB is not evenly distributed among the U.S. population. Cases occur disproportionately in urban areas, in conditions of poverty and over-crowding, and among racial and ethnic minorities and foreign-born persons. In 2012, 63% of the U.S. TB cases occurred among foreign-born persons (43% in Georgia).

- The average lifetime risk of developing active TB following TB infection, if no treatment of latent TB infection is received, is approximately 10% (5% in the first two years after tuberculin skin test conversion [new infection] and 5% in the remaining lifetime). UNAIDS estimates that persons infected with both TB and HIV are 30 to 50 times more likely to develop TB disease than those infected with TB but who do not have HIV infection (10% per year risk of progression to active TB disease among people living with HIV who have LTBI).

Number of TB Cases
City of Atlanta, Metro Atlanta, Georgia
1993-2012

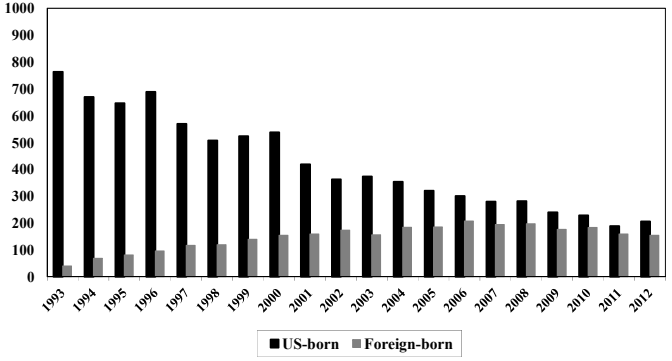


- Drug resistant TB is a major challenge to global TB control and associated with higher morbidity and mortality compared to drug susceptible disease. The treatment of highly drug-resistant *M. tuberculosis* requires longer, more complex and expensive treatment regimens. Multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid (INH) and rifampin (RIF); extensively drug resistant (XDR-TB) is defined as MDR-TB plus resistance to a fluoroquinolone drug plus an injectable drug (kanamycin, amikacin, and/or capreomycin). Treatment regimens are complicated with many potential adverse effects and require up to 24 months of treatment.

- The State of Georgia has had TB rates higher than the U.S. average for the last quarter of a century. In 2012, Georgia had 359 new TB cases (3.6 per 100,000 population). Of the culture confirmed TB cases tested for drug susceptibility in Georgia in 2012, 10% had primary resistance to INH, three had primary resistance to RIF (1%) and one (0.3%) was MDR.

- Half (50%) of TB cases in Georgia occurred in four counties within the metropolitan Atlanta area in 2012 (DeKalb, Gwinnett, Fulton and Cobb).

US-born and Foreign-born TB Cases
Georgia
1993-2012



III. Diagnostic Tests for Latent TB Infection

There is no "gold standard" test for latent TB infection (LTBI). Two types of diagnostic tests to detect LTBI are now available. This includes the tuberculin skin test (TST) which has been around for >100 years and a new generation of diagnostic tests, the interferon-γ release assays (IGRAs), which are T-cell based invitro blood tests. Two IGRAs are now approved for use by the U.S. FDA. Neither the TST nor IGRA tests can distinguish LTBI from active TB disease.

A. Tuberculin Skin Test (TST).

The TST measures a delayed type hypersensitivity reaction (recruitment of memory T cells to the site of an intradermal injection of purified protein derivative [PPD]). The TST should be carried out using the Mantoux method. Multiple puncture tests (Tine and Heaf) should **not** be used. Tuberculin skin tests should be administered and read by trained healthcare personnel. The tuberculin skin test (TST) is administered by injecting 0.1 ml of 5 tuberculin units (TU) of PPD into the dorsal or volar surface of the forearm. The injection is made with a disposable tuberculin syringe, with the needle bevel facing upward and placed just under the surface of the skin, so that a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter is produced.

Needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. Dispose of needles and syringes in puncture-resistant containers. Follow standard precautions for infection control.

TSTs should be read 48 to 72 hours after administration. If test reading is delayed, a positive reaction may still be measurable up to one week after testing. A test cannot be read as negative if more than 72 hours have passed since it was placed. The transverse diameter of palpable **induration** should be measured and **recorded in millimeters**. If no induration is present, record "0 mm". Do not measure erythema (redness).

Limitations of the TST include cross reactions between TST and BCG and non-tuberculous mycobacteria. Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG but an advantage of the IGRAs are that they do not cross react with BCG (see below). A positive TST in a BCG-vaccinated person is assumed to indicate infection with *M. tuberculosis* when the person tested is at increased risk for recent infection, is from an area with high rates of TB, or has medical conditions that increase the risk for disease (Section III, B).

B. Criteria for a Positive Tuberculin Test, by Risk Group

Reaction ≥ 5 mm of induration

- Human immunodeficiency virus (HIV)-seropositive persons
- Recent contact of an infectious TB case
- Fibrous changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/d of prednisone for 1 month or more including patients who will receive TNF-α inhibitors)

Reaction ≥ 10 mm of induration

- Recent immigrants to the U.S. (within the last 5 years) who came from high TB incidence countries
- Injection drug users
- Residents and employees of the following high-risk congregate settings: prisons and jails, nursing homes, hospitals, residential facilities for persons with HIV/AIDS and homeless shelters
- Mycobacteriology laboratory personnel
- Persons with the following clinical conditions that place them at risk of progression from latent TB infection to active TB disease: silicosis, diabetes mellitus, chronic renal failure, leukemia and lymphoma, carcinoma of the head, neck or lung, weight loss of ≥ 10% of ideal body weight, gastrectomy, and

jejunoileal bypass

- Children < 5 yrs of age or infants, children, and adolescents exposed to adults at high-risk
- Recent TST conversion (increase of ≥10 mm of induration within the past 2 years)

Reaction ≥ 15 mm of induration

- Persons with no risk factors for TB
- Persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥ 15 mm is considered positive

C. Two-Step Testing and the Booster Reaction

In some persons (especially individuals > 50 years of age) with LTBI, delayed-type hypersensitivity reactions to tuberculin may wane over time. When skin tested years after infection occurred, these persons may have a negative tuberculin skin test reaction. However, this test may stimulate (boost) their ability to react to subsequent tuberculin testing, causing a positive reaction to subsequent tuberculin skin tests. The boosted reaction represents a true positive result, but not a true conversion due to recent infection. Two-step tuberculin skin testing is used to distinguish between boosted reactions and reactions due to new infection.

Two-step testing (at baseline) is recommended for employees or residents in institutional settings (such as health care workers or correctional institution employees) who will undergo routine, serial tuberculin screening (and have not had a TST in the past year), and for whom it is important to distinguish between new infection and boosted reaction from past infection.

Two-Step Testing

1. Place the first test with 0.1 ml (5 TU) of tuberculin.
2. If the reaction to the first test is negative, give a second test with the same dose and strength of tuberculin, 1-3 weeks later. (If the reaction to the first test is positive, consider the person infected and there is no need for a second test.)
3. If the second test is positive, consider the person infected.
4. If the second test is negative, consider the person uninfected.
5. Individuals who have a positive reaction to either test require a follow-up evaluation with chest x-ray.
6. For individuals who will undergo serial testing (e.g., annual tuberculin testing), two-step testing is required for only the first test, to establish a baseline negative test. Subsequent tuberculin testing should be only one test.

D. Anergy Testing

Anergy testing is not recommended for routine use in persons living with HIV or otherwise immunocompromised. Factors limiting the usefulness of anergy skin testing include problems with the standardization and reproducibility, the low risk for TB disease associated with a diagnosis of anergy, and the lack of apparent benefit of treatment of LTBI for groups of anergic HIV-infected persons in the U.S.

E. Interferon-γ Release Assays (IGRAs)

Two FDA-approved IGRA tests are commercially available in the U.S. These include the QuantiFERON-TB Gold in Tube (QFT) test and the TSPOT.TB (TSPOT) test. Guidelines on this use of these IGRAs as diagnostic tests for LTBI have been published by CDC [MMWR 2010; 59 (No. RR-5):1-26] but the recommendations are not evidence rated. IGRAs are in-vitro blood tests that are based on interferon-γ release (IFN-γ) after stimulation by relatively TB specific antigens (e.g., ESAT-6 and CFP-10 in both assays and the addition of TB7.7 in QFT). The QFT is a whole blood assay that uses an ELISA technique to measure IFN-γ production. TSPOT uses peripheral blood mononuclear cells (PBMCs) and detects (by use of ELISPOT) the number of T cells producing IFN-γ. Because the antigens used in the IGRAs are not found in *M. bovis* BCG (or most non-tuberculous mycobacteria), the IGRAs are more specific than the TST when used to test persons who have received BCG vaccination and do not cross react with most non-tuberculous

mycobacteria. Criteria on what constitutes a positive IGRA test have been published and are shown in Tables 1 and 2. The cut-off points are static and there are no criteria for what constitutes an IGRA conversion when serial testing is performed. IGRAs can provide a positive, negative, or indeterminate result. Indeterminate results more commonly occur among HIV-seropositive and other immunocompromised persons but can occasionally occur among healthy individuals. If the result of the IGRA test is indeterminate, it is recommended that the test be repeated. The risk of developing active TB after a positive TST result has been defined in large prospective longitudinal studies. There are limited or no such equivalent data for the IGRAs. Thus far, quantitative results from IGRAs (i.e., the degree of positivity) have not been shown to have prognostic value in predicting increasing risk of progression to active TB and therefore should not be used for that purpose in clinical practice. The IGRAs cost significantly more per test than the TST but are logistically easier to perform as they only require a single visit. In certain situations or selected populations (e.g., BCG-vaccinated persons), IGRAs may be cost-effective when taking into account cost of chest radiographs avoided compared to the TST when cross reactions may be seen.

Table 1. Interpretation Criteria for the QuantiFERON-TB Gold In-Tube Test (QFT-GIT)[1]

Interpretation	Nil*	TB Response†	Mitogen Response§
Positive¶	≤8.0	≥0.35 IU/ml and ≥25% of Nil	Any
Negative**	≤8.0	<0.35 IU/ml or <25% of Nil	≥0.5
Indeterminate††	≤8.0	<0.35 IU/ml or <25% of Nil	<0.5
	>8.0	Any	Any

Source: Based on manufacturer recommendations for QuantiFERON-TB Gold In-Tube [Package insert]. Available at: http://www.cellestis.com/IRM/content/pdf/QuantiFeron%20US%20VerG–Jan2010%20NO%20TRIMS.pdf.

* The interferon gamma (IFN-γ) concentration in plasma from blood incubated without antigen.

† The IFN-γ concentration in plasma from blood stimulated with a single cocktail of peptides representing early secretory antigenic target-6 (ESAT-6), culture filtrate protein-10 (CFP-10), and part of TB 7.7 minus Nil.

§ The IFN-γ concentration in plasma from blood stimulated with mitogen minus Nil.

¶ Interpretation indicating that *Mycobacterium tuberculosis* infection is likely.

** Interpretation indicating that *M. tuberculosis* infection is not likely.

†† Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection.

[1]From: MMWR 2010;59(RR-5):1-25

Table 2. Interpretation Criteria for the T-SPOT.TB Test (T-Spot)[1]

Interpretation	Nil*	TB Response†	Mitogen§
Positive¶	≤10 spots	≥8 spots	Any
Borderline**	≤10 spots	5, 6, or 7 spots	Any
Negative††	≤10 spots	≤4 spots	
Indeterminate**	>10 spots	Any	Any
	≤10 spots	<5 spots	<20 spots

Source: Based on Oxford Immunotec Limited. T-Spot.TB [Package insert]. Available at: http://www.oxfordimmunotec.com/USpageInsert.\

* The number of spots resulting from incubation of PBMCs in culture media without antigens.

† The greater number of spots resulting from stimulation of peripheral blood mononuclear cells (PBMCs) with two separate cocktails of peptides representing early secretory antigenic target-6 (ESAT-6) or culture filtrate protein-10 (CFP-10) minus Nil.

§ The number of spots resulting from stimulation of PBMCs with mitogen without adjustment for the number of spots resulting from incubation of PBMCs without antigens.

¶ Interpretation indicating that *Mycobacterium tuberculosis* infection is likely.

** Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection.

†† Interpretation indicating that *M. tuberculosis* infection is not likely.

[1]From: MMWR 2010;59(RR-5):1-25

F. Targeted Testing and Diagnostic Tests for LTBI

Diagnostic testing for LTBI should be targeted at those who are at **increased risk** for having LTBI and in some situations at those who if infected with *M. tuberculosis* are at increased risk of progression to active TB disease (see page 17 and Table 3). HIV-infected persons with LTBI have the greatest risk of progressing to active TB (at rates up to 10% per year). All persons with **HIV-infection** should undergo testing for LTBI and if LTBI is found should strongly be encouraged to initiate and complete treatment for LTBI. Patients who take **immunomodulating drugs** are also at very high risk for progression to active TB if infected with *M. tuberculosis*. This includes patients with LTBI who are treated with TNF-α inhibitors such as infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), certolizumab pegol (Cimzia), or golimumab (Simponi). Following the initial introduction of TNF-α inhibitor drugs there were reports of the subsequent development of extrapulmonary and disseminated disease and in some cases death. All patients who will be treated with TNF-α inhibitor drugs should be screened for LTBI before starting the medication; if found to have LTBI, they should be started on therapy for LTBI (after active TB is excluded) before starting the TNF-α inhibitor. Whether treatment for LTBI should be completed before a TNF-α inhibitor is started is controversial. Patients preparing to receive a **solid organ transplant** should also be screened for LTBI**.** Children less than 5 years of age are at increased risk for progression to active TB disease if infected, but should not be tested for LTBI unless they are at increased risk for TB exposure (see page 18). Persons who recently

converted to a positive skin test should be medically evaluated and active TB disease ruled out (see section III.G. page 21) and LTBI treatment considered. Although, persons with a chest radiograph suggestive of old TB are at increased risk for progression to active TB disease they should not be retested for LTBI.

Who should be targeted for LTBI testing?[1]

Diagnostic tests for LTBI are not recommended for people with low risk of infection with *M. tuberculosis*. Certain persons with increased risk of developing TB if they have LTBI should be targeted for testing. These include:

- People who have spent time with someone who has TB disease (contacts of active TB cases)
- People living with HIV or those who have other immune compromising illnesses
- Immigrants from a country where TB disease is common (most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia)
- People who live or work somewhere in the United States where TB disease is more common (homeless shelters, prison or jails, or some nursing homes)
- People who use illegal drugs
- People who are preparing to initiate treatment with a TNF-α inhibitor.
- People preparing to receive a solid organ transplant.

[1]From: MMWR 2010;49(No.RR-6)

Testing of low risk individuals for LTBI is discouraged because false positive results are more likely to occur in this setting. Because QFT, TSPOT, and TST each measure different aspects of the immune response and use different antigens and interpretation criteria, test results might not be interchangeable. Different tests can yield different results. Studies which employed multiple diagnostic tests have demonstrated that discordant test results are not uncommon.

Table 3. High Prevalence and High Risk Groups[1]

Groups with a High-prevalence of Latent TB Infection	Groups with a High Risk of Progression to Active TB Disease if infected with *M. tuberculosis*
Persons born in countries with high prevalence of TB	Children less than 5 yr of age
	Persons with HIV coinfection
Groups with poor access to healthcare	Persons who are close contacts of persons with infectious TB
Persons who live or spend time in certain facilities (e.g. nursing homes, correctional institutions, homeless shelters, drug treatment centers)	Persons whose tuberculin skin test results converted to positive in the past 1-2 yr
	Persons who have chest radiographs suggestive of old TB
Persons who inject drugs	Persons with certain medical conditions*

*Diabetes mellitus, silicosis, prolonged therapy with corticosteroids, immunosuppressive therapy particularly TNF-α blockers, leukemia, Hodgkin's disease, head and neck cancers, severe kidney disease, certain intestinal conditions, malnutrition

[1]***From: MMWR 2010;59(RR-5):1-25***

Which diagnostic test for LTBI should be used?

General Recommendations for Use of Diagnostic Tests for LTBI:

- CDC guidelines note that either a TST or FDA-approved IGRA (i.e. QFT or TSPOT) can be used for diagnostic testing and use of either test is an acceptable medical and public health practice. **As noted below, there are preferences and special circumstances in which one of these tests is preferred**.
- CDC guidelines note an IGRA may be used in place of a TST in all situations in which they recommend tuberculin skin testing as an aid in diagnosing *M. tuberculosis* infection.

Situations in which an IGRA is preferred but a TST is acceptable:

- Testing of BCG-vaccinated persons (because of improved specificity of the IGRA vs. TST in this population)
- Testing of persons who may be unlikely to return to have the TST read (e.g., homeless individuals and injection drug users or those with substance abuse)

Situations in which a TST is preferred but an IGRA is acceptable:

- Testing children aged $\leq$ 5years (TST is recommended by the American Academy of Pediatrics)
- Serial testing (e.g., health care workers). While not a CDC recommendation, we recommend that the TST be used for serial testing programs. Recent reports have indicated very high rates of diagnostic test "conversion" (e.g., up to 10-fold higher than the TST) when IGRAs were used for serial testing of health care

workers in low risk/low prevalence situations (thus suggesting the IGRA results were false positive). In addition, the Canadian Tuberculosis Committee has concluded that there is insufficient published evidence to recommend serial IGRA testing in health care workers and other populations.

Situations in which a TST or IGRA may be used without preference:

- Contact investigations (i.e., testing of recent contacts of persons known or suspected to have active TB).

Situations in which testing with ***both* an IGRA and a TST may be considered:**

- When additional evidence of infection is required to encourage a person that they have LTBI and should take and adhere to therapy for LTBI (e.g., foreign born health care worker who believes that their positive TST result is attributable to BCG)
- When the initial diagnostic test performed in a healthy person at low risk for both infection and progression is positive (and thought to be a false positive). This situation could be prevented by using targeted testing and not testing low risk individuals.
- Repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline, or invalid and a reason for testing persists.
- In very high risk individuals when missing the presence of LTBI could have serious consequences (e.g., individuals to be started on TNF-α blockers or other immunocompromising

medications).

G. Medical Evaluation after Testing for LTBI

- **Neither an IGRA nor a TST can distinguish LTBI from active TB disease.** A negative IGRA or TST does not rule out active TB disease.

- Persons with a positive TST or IGRA should be evaluated for the likelihood of *M. tuberculosis* infection, for risks for progression to active TB if infected and for symptoms and signs of active TB.

- **A diagnosis of LTBI requires that active TB be excluded by medical evaluation** which should include taking a medical history and a physical exam to check for suggestive symptoms and signs, a chest x-ray, and when indicated, testing of sputum or other clinical samples for the presence of *M. tuberculosis*.

- Persons with a newly documented diagnostic test for LTBI (positive TST or IGRA) should have a chest x-ray performed to ensure that they do not have active TB disease. After an initial negative chest x-ray, **no routine follow-up chest x-rays are necessary**. Persons with a positive diagnostic test for LTBI should be educated about the signs and symptoms of active TB disease and instructed to consult with a physician if these symptoms occur.

- In healthy persons who have a low likelihood both of *M.*

tuberculosis infection and of progression to active TB disease if infected, a single positive IGRA or TST result should not be taken as reliable evidence of *M. tuberculosis* infection. Because of the low probability of infection, a false-positive result is more likely. In such situations, the likelihood of *M. tuberculosis* infection and of disease progression should be reassessed, and the initial test results should be confirmed. Repeat testing, with either the initial test or a different test, may be considered on a case-by-case basis. For such persons, an alternative is to assume, without additional testing, that the initial result is a false positive. This becomes somewhat complex because of the lack of a "gold standard" diagnostic test for LTBI. For healthy persons who have a low risk for both infection and progression, discounting an isolated positive result as a false positive may be reasonable. This will increase detection specificity and decrease unnecessary treatment.

- In persons with **discordant test results** (i.e., one positive and the other negative), decisions about medical or public health management require individualized judgment in assessing the quality and magnitude of each test result (e.g., size of induration and presence of blistering for a TST; and the TB Response, Nil, and Mitogen values for an IGRA), the probability of infection, the risk for disease if infected, and the risk for a poor outcome if disease occurs. Patients who are at high risk for progression to active TB when LTBI is present (e.g., HIV-infected persons, those scheduled to begin a TNF-α inhibitor, children < 5 years)

should be assumed to have LTBI if one diagnostic test is positive (even if there are discordant results). For persons who have received BCG and who are not at increased risk for a poor outcome if infected, TST reactions of <15 mm in size may reasonably be discounted as false positives when an IGRA is clearly negative. In other situations, inadequate evidence exists on which to base recommendations for dealing with discordant results. Consultation with a TB expert should be considered when discordant results are present.

- Persons with a positive diagnostic test for LTBI who have active TB excluded, should be considered for treatment of LTBI. Treatment of LTBI is recommended for those at increased risk of progression to active TB disease (see Table 3). Treatment regimens for LTBI are described below.

H. Reporting of Pediatric Positive tests for LTBI

Latent TB infection (LTBI) in children indicates recent transmission of TB in the community. Also, young children who are infected with TB are at high risk of progressing to TB disease. Because of the extreme importance of identifying children who have been exposed to and infected with TB, **LTBI in a child less than 5 years old is a notifiable disease in the state of Georgia**. Cases may be reported electronically at http://sendss.state.ga.us, by calling 1-866-782-4584, or by calling your local health department.

IV. Treatment of Latent TB Infection (LTBI)

Treatment of LTBI is recommended for patients at increased risk for developing active TB disease. Those at increase risk for developing active TB disease following infection with *M. tuberculosis* include HIV-infected persons, those receiving immunosuppressive therapy (or scheduled to receive immunosuppressive therapy including TNF-α inhibitors), children <5 years old, those with diabetes or chronic renal failure on hemodialysis, close contacts of patients with recent pulmonary TB, or those who have converted from a negative to a positive diagnostic test for LTBI (TST or IGRA) within the previous 2 years. The risk of serious disease, including miliary or disseminated TB and tuberculous meningitis, is highest among patients with HIV infection. Infants, the elderly, and patients with other causes of severe immunosuppression are also at increased risk. Treatment for LTBI should be started only if clinical and radiographic evaluations exclude active TB disease. Persons with LTBI who are considered to be at high risk for developing active TB should be offered (and encouraged to take) treatment for LTBI irrespective of age.

A. Treatment Regimens

Treatment regimens for LTBI are outlined in Table 4. Several different regimens are recommended by the CDC and American Thoracic Society (ATS). These include:

1. Isoniazid (INH). INH for 9 months is standard therapy for the treatment of LTBI in adults and is the preferred treatment for LTBI

among children <12 years of age (due to presumed infection with a drug susceptible isolate). A six month regimen of INH is an alternative regimen in HIV-seronegative adults.

2. Rifampin. Rifampin for 4 months (6 months in children) is an alternative regimen for the treatment of LTBI (e.g., among persons infected with INH-resistant strains) and may also be used as an alternative regimen for persons presumed to be infected with a drug-susceptible (i.e., INH-susceptible) strain. The efficacy of this shorter regimen compared to 9 months of isoniazid has not been established, but it has improved adherence and may have fewer adverse effects

3. INH plus Rifapentine (RPT). A short course regimen of **weekly** INH plus rifapentine for 12 weekly doses (given by directly observed therapy [DOT]) has recently been recommended as an equal alternative to 9 months of INH for treatment of LTBI for adults and children $\geq$12 years of age, including HIV-infected patients not taking antiretrovirals. This regimen is NOT recommended for HIV-infected persons taking antiretroviral drugs, pregnant women (or those expecting to become pregnant), children <2 years old, or patients infected with suspected INH-resistant, rifampin-resistant or MDR isolates.

Because of the marked increase risk of hepatotoxicity (compared to INH or rifampin alone), rifampin plus pyrazinamide [2 month short course regimen] is NOT recommended for the treatment of LTBI although these drugs remain an important component of a multidrug regimen in the treatment of active TB disease.

USPHS/IDSA EVIDENCE BASED RATING SYSTEM FOR THE STRENGTH OF TREATMENT RECOMMENDATIONS AND QUALITY OF EVIDENCE

Strength of the recommendation

A. Preferred; should generally be offered
B. Alternate; acceptable to offer
C. Offer when preferred or alternative regimens cannot be given
D. Should generally not be offered
E. Should never be given

Quality of evidence supporting the recommendations

I. At least one randomized trial with clinical end points
II. Clinical trials that either are not randomized or were conducted in other populations
III. Expert opinion

Table 4. Summary of LTBI Treatment Guidelines[1]

Drugs	Duration	Interval	Rating (Evidence) HIV-	HIV+
Isoniazid	9 mo	Daily	A (II)	A (II)
		Twice weekly	B (II)	B (II)
Isoniazid	6 mo	Daily	B (I)	C (I)
		Twice weekly	B (II)	C (I)
Rifampin	4 mo	Daily	B (II)	B (III)
*Rifampin-pyrazinamide	2 mo 2-3 mo	Daily Twice weekly	D (II) D (III)	D (II) D (III)
Isoniazid-rifapentine	12 wks	Once weekly	A (I)	

[1]*Adapted from: MMWR 2003;52: 735-739 and MMWR 2011;60: 1650-3.*

***Our Recommendation is DO NOT USE rifampin-pyrazinamide (RIF-PZA) for LTBI**

Recommended regimens, dosages, length of therapy and number of doses for LTBI therapy are listed in Tables 5 and 6 on pages 28 – 31.

Table 5. Treatment of LTBI – Recommended Drug

Drug	Interval and Duration	Adult Dosage	Criteria for Completion
Isoniazid* (INH)	Daily self-adm** for 9 months	300 mg PO (5 mg/kg - Maximum Dose 300 mg)	270 doses within 12 months
	Daily DOT for 9 months ♦	300 mg PO (5 mg/kg - Maximum Dose 300 mg)	190 doses within 12 months
	Twice-weekly DOT for 9 months	900 mg PO (15 mg/kg - Maximum Dose 900 mg)	76 doses within 12 months
Rifampin (RIF)	Daily self-adm** for 4 months (18 weeks)	600 mg PO (10 mg/kg - Maximum Dose 600 mg)	120 doses within 6 months
	Daily DOT for 4 months (18 weeks) ♦	600 mg PO (10 mg/kg - Maximum Dose 600 mg)	90 doses within 6 months
Isoniazid (INH)* and Rifapentine (RPT)	Once weekly by DOT for 12 doses (12 weeks)	Isoniazid: 15 mg/kg PO (rounded up to the nearest 50 or 100 mg); 900 mg PO maximum Rifapentine: 10.0-14.0 kg 300 mg PO 14.1-25.0kg 450 mg PO 25.1-32.0 kg 600 mg PO 32.1-49.9 kg 750 mg PO ≥50 kg 900 mg (maximum dose) PO	11 doses within 16 weeks (doses may be given no more frequently than every 72 hours)

* Pyridoxine (Vitamin B6) 25 – 50 mg is recommended to be given with each dose of INH (in patients with normal renal function) as a preventive measure against INH-induced peripheral neuropathy. ** Daily self-administered = 7 days/week ♦ Daily DOT = 5 days/week (Monday through Friday)

LTBI Treatment Regimens for Adults (≥16 years of age)

Comments
In HIV-infected persons, INH may be taken concurrently with antiretroviral agents including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, or integrase inhibitors. *If twice-weekly dosing is used for INH, it must be given by DOT.* The twice weekly regimen of INH for treatment of LTBI is NOT recommended for HIV-infected persons with LTBI. *Once weekly dosing of INH plus rifapentine must be given by DOT.* *Pyridoxine is recommended for those taking INH to prevent INH-induced peripheral neuropathy.*
Rifampin is recommended for the treatment of LTBI in persons who are contacts of TB cases with proven or suspected INH-resistant, rifampin susceptible TB but may also be used in other persons with LTBI (e.g., contacts on drug susceptible TB cases and unknown contacts when rifampin resistant or MDR-TB is not suspected).
INH and RPT is recommended as an equal alternative to 9 months of daily self-administered INH for treating LTBI in otherwise healthy persons (12 years and older) at high risk for developing active TB. This includes close contacts of active TB cases, recent converters, HIV-infected persons NOT on antiretroviral agents, and persons with old healed TB on chest x-ray. INH and RPT may also be used in situations where it offers practical advantages or for individuals unlikely to complete 9 months of daily INH. INH and RPT is NOT recommended for the following groups: children aged <2 years, because the safety and pharmacokinetics of RPT have not been established; HIV-infected patients receiving antiretroviral treatment, because the drug interactions have not been studied; pregnant women or women expecting to become pregnant during treatment, because safety in pregnancy is unknown; and patients who have LTBI with presumed INH or RIF resistance or MDR resistance.

adm = administered; MDR = multidrug resistant (resistance to at least both INH and RIF)
NOTE: Isoniazid is available in 100 and 300 mg tablets (both are scored for dividing in half (½). Rifapentine is available in 150 mg tablets only.

Table 6. Treatment of LTBI - Recommended Drugs

Drug	Interval and Duration	Dosage	Criteria for Completion
Isoniazid (INH) *	Daily self-adm** for 9 months (39 weeks)	10-15 mg/kg PO (Maximum Dose 300mg)	270 doses within 12 months
	Daily DOT ♦ for 9 months (39 weeks)	10-15 mg/kg PO (Maximum Dose 300mg)	190 doses within 12 months
	Twice-Weekly DOT for 9 months (39 weeks)	20-30 mg/kg PO (Maximum Dose 900mg)	76 doses within 12 months
Rifampin	Daily self-adm** for 6 months (26 weeks)	10-20 mg/kg PO (Maximum Dose 600mg)	180 doses within 9 months
	Daily DOT ♦ for 6 months (26 weeks)	10-20 mg/kg PO (Maximum Dose 600mg)	130 doses within 9 months
Isoniazid (INH)* and Rifapentine (RPT)	Once weekly by DOT for 12 doses (12 weeks)	Isoniazid: 15 mg/kg PO rounded up to the nearest 50 or 100 mg; 900 mg PO maximum Rifapentine: 10.0-14.0 kg 300 mg PO 14.1-25.0kg 450 mg PO 25.1-32.0 kg 600 mg PO 32.1-49.9 kg 750 mg PO Equal to or over 50.0 kg 900 mg (Maximum dose) PO	11 doses within 16 weeks (doses may be given no more frequently than every 72 hours)

adm = administered; MDR = multidrug resistant (resistance to at least both INH and RIF)
* Pyridoxine (Vitamin B6) 25 mg is recommended to be given with each dose of INH (in patients with normal renal function) to prevent INH-induced peripheral neuropathy. **Daily self administrated (adm) = 7 days/week; ♦ Daily DOPT = 5 days/week (Monday through Friday).

Regimens for Children (from birth through 15 years)

Comments
Isoniazid for 9 months is the preferred regimen for children < 12 years of age. *DOT must be used with twice-weekly dosing.* The twice weekly regimen of INH for treatment of LTBI is NOT recommended for HIV-infected persons. * Pyridoxine (Vitamin B6) 25 mg is recommended to be given with each dose of INH (in patients with normal renal function) to prevent INH-induced peripheral neuropathy.
Rifampin is recommended for the treatment of LTBI in persons who are contacts of TB cases with proven or suspected INH-resistant, rifampin susceptible TB but may also be used in other persons with LTBI (e.g. INH susceptible contacts, unknown contacts when rifampin resistant or MDR-TB is not suspected). INH is preferred therapy for LTBI in children < 12 years of age when INH resistance in the source patient is not suspected.
INH and RPT is recommended as an equal alternative to 9 months of daily self-administered INH for treating LTBI in otherwise healthy persons (≥12 years of age) at high risk for developing active TB. This includes close contacts of active TB cases, recent converters, HIV-infected persons NOT on antiretroviral agents, and persons with old healed TB on chest x-ray. The INH-RPT regimen is not recommended by CDC for use in children <12 years of age. Consult with a TB expert if this regimen is considered for use in the treatment of LTBI for children aged 2 through 11 years of age who are close contacts for whom the INH and RPT regimen may be considered because it offers practical advantages or because the child is unlikely to complete 9 mo of daily INH. INH and RPT should NOT recommended for the following patients: children age <2 years; HIV infected persons receiving antiretroviral treatment; pregnant women or women expecting to become pregnant during treatment; and patients who have LTBI with presumed INH or RIF resistance or multidrug resistance (MDR).

NOTE 1: INH is available in 100 and 300 mg tablets (both are scored for dividing in half (½). Rifapentine is available in 150 mg tablets only. NOTE 2: Directly Observed Therapy (DOT) is required for all children with LTBI <5 years of age and those receiving ANY intermittent dosing regimen. Directly Observed Therapy (DOT) is recommended for all children up to the age of 15 years.

NOTE 3: One month is 4.3 weeks.

Table 7. LTBI Treatment Drug Adverse Reactions

Drug	Adverse Reactions	Monitoring	Comments
Isoniazid (INH)	Gastrointestinal (GI) upset, hepatic enzyme elevations, hepatitis, peripheral neuropathy, mild effects on central nervous system, drug interactions	Baseline measurements of AST for adults. Repeat measurements if: * baseline results are abnormal * client is at high-risk for adverse reactions * client has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption. Pyridoxine can prevent isoniazid-induced peripheral neuropathy.
Rifampin (RIF) and Rifapentine (RPT)	Orange discoloration of body fluids (secretions, tears, urine), GI upset, drug interactions, hepatitis, thrombocytopenia, rash, fever, influenza-like symptoms, hypersensitivity reaction* Many drug-drug interactions	Complete blood count, platelets and liver function tests. Repeat measurements if: * baseline results are abnormal * client has symptoms of adverse reactions Prior to starting RIF or RPT: need to carefully review all medications being taken by the patient with LTBI and ensure there is no contraindication to the use of that medication and RIF or RPT.	Hepatitis risk increases with age and alcohol consumption. Rifampin monotherapy may be associated with lower risk of hepatotoxicity compared to INH monotherapy for patients being treated for LTBI. Need to carefully review for possible drug-drug interactions prior to starting RIF or RPT and ensure there are no contraindications to these agents prior to using them for the treatment of LTBI.

** Hypersensitivity reaction to rifamycins (rifampin or rifapentine): reactions may include a flu like syndrome (e.g. fever, chills, headaches, dizziness, musculoskeletal pain), thrombocytopenia, shortness of breath or other signs and symptoms including wheezing, acute bronchospasm, urticaria, petechiae, purpura, pruritus, conjunctivitis, angioedema, hypotension or shock. If moderate to severe reaction (e.g. thrombocytopenia, hypotension), hospitalization or life-threatening event: Discontinue treatment. If mild reaction (e.g. rash, dizziness, fever): Continue to monitor patient closely with a low threshold for discontinuing treatment.*

B. Monitoring of Patients on Treatment for LTBI

For all patients:

- Initial clinical evaluation and baseline ALT (or AST) on all adult patients who will be receiving treatment for LTBI
- Follow-up clinical evaluations **at least monthly** if receiving INH or RIF alone; for those on self-administered therapy, never dispense more than one month of therapy (and no refills)
- Include careful questioning about side effects and a brief physical examination checking for evidence of hepatitis or other side effects
- Educate patients about side effects associated with LTBI treatment (see Table 7)
- Advise patients to stop treatment and promptly seek medical evaluation if adverse effects shown in Table 7 occur.
- If side effects occur, evaluate promptly and change (i.e., discontinue) treatment if indicated
- CDC guidelines state routine monthly monitoring of hepatic enzymes ("liver function tests") are not generally indicated with INH or RIF-only treatment unless risk factors present for increase risk of hepatotoxicity. We recommend baseline liver function tests (LFTs) in all adults prior to initiating treatment for LTBI. Consider monthly ALT (or AST testing) in adults.
- In the absence of liver disease or HIV infection, children on LTBI do not need monthly ALT (or AST) monitoring.

Indications for regular monthly monitoring of LFTs:

- Abnormal ALT (or AST) at baseline
- HIV infection
- Pregnancy
- First three months postpartum
- Chronic liver disease (including HCV infection)
- Regular alcohol use
- Patients on other drugs which are potentially hepatotoxic
- Advanced age

Medication should be discontinued and patient evaluated if:

- Transaminase levels > 3 times upper limit of test in presence of symptoms of adverse events
- Transaminase levels > 5 times upper limit of test in asymptomatic patient

Pyridoxine (Vitamin B_6) should be used (25-50 mg/day) with INH for persons with conditions in which neuropathy is common (e.g., HIV, diabetes, alcoholism, malnutrition) as well as pregnant women and persons with a seizure disorder to prevent isoniazid-associated neuropathy. It should be given to all HIV-infected persons, all children, and women who are breastfeeding. For healthy individuals on a normal diet, pyridoxine is optional. However, we prefer to give pyridoxine to all patients on INH. Pyridoxine (at 25 mg per day) is also recommended for children on INH.

C. Contacts of MDR-TB Cases (i.e., cases resistant to at least isoniazid and rifampin)

In deciding how to treat persons with latent TB infection which may be due to infection with a MDR-TB strain, the following four questions should be considered. **A TB specialist should be consulted in the management of contacts to MDR-TB cases**.

- **How likely is it that a patient is newly TB infected?** A patient with a documented positive prior TST (or other diagnostic test such as an IGRA) is much less likely to be newly infected.
- **How likely is it that the patient is infected with an MDR-TB strain?** An infant with a positive diagnostic test for LTBI (TST or IGRA) whose parent has active MDR-TB is highly likely to be infected with MDR-TB. In contrast, a health care worker with a positive TST and no known source case may have a low probability of being MDR-TB infected.
- **How likely is the patient to develop active TB?** Those at highest risk include infants and persons who are HIV infected or otherwise immunocompromised.
- **What is the drug-susceptibility pattern of the source patient's isolate?** Treatment of LTBI must be tailored to the susceptibility pattern of the source patient's isolate. When the source patient is known to have isoniazid-resistant TB, rifampin may be used for treatment of LTBI. There are no evidence-based guidelines for the treatment of LTBI when an individual is thought to be infected with a MDR-TB strain. In some cases of MDR-TB or XDR-TB, no LTBI regimen is available.

V. Treatment of Current (Active) Disease (Classes III & IV)

A. Considerations

1) The **provider (or public health program if this is the site of treatment)** is responsible for prescribing an appropriate treatment regimen ***and*** ensuring that treatment is completed successfully. It is strongly recommended that TB treatment be undertaken in consultation with a physician who is well versed and experienced in its management.

2) In general, **initiate therapy with a four drug regimen** (INH, RIF, PZA, EMB) as described on pages 40-58 (Tables 8 and 10). A number of different treatment options are available as outlined in Tables 8 and 10 and discussed in further detail below.

3**) DIRECTLY OBSERVED THERAPY (DOT) IS THE STANDARD OF CARE FOR ALL PATIENTS WITH ACTIVE TUBERCULOSIS DISEASE TO FACILITATE ADHERENCE AND COMPLETION OF THERAPY.** DOT can be given by the patient's local county public health department.

Patient-centered care (also called enhanced DOT) is encouraged for all patients. Treatment is tailored and supervised based on each patient's clinical *and* social circumstances. TB treatment is most successful within a comprehensive framework that addresses both clinical *and* social issues of relevance to the patient.

4) Drug susceptibility testing should be performed on initial *M. tuberculosis* isolates in ALL cases. Drug susceptibility testing and AFB cultures are performed by the Georgia Public Health

Laboratory (Phone: 404-327-7944 or 404-327-7945). Repeat susceptibility testing should be performed on *M. tuberculosis* isolates for patients who do not respond to therapy or who have a positive culture after two months of therapy.

5) The best way to measure the effectiveness of therapy for pulmonary TB is to monitor patients bacteriologically through sputum examination *at least monthly* until two consecutive negative cultures are obtained. We recommend obtaining monthly sputum examinations throughout the course of therapy. **For patients with pulmonary TB, it is essential to obtain a sputum culture after two months of therapy.**

Patients with drug-susceptible cavitary pulmonary TB who have a positive sputum culture after two months of therapy are at increased risk for relapse after six months of therapy; a positive culture after two months of therapy impacts recommendations for the total length of therapy. Patients being treated for uncomplicated pulmonary TB do not require frequent chest x-rays; bacteriologic examination is far more important than monitoring chest films.

6) If a patient's sputum cultures remain positive beyond two months of therapy, the possibility of drug-resistant disease, malabsorption, or patient failure to take medications as prescribed should be considered. Drug susceptibility studies should be repeated, and if not already on directly observed therapy (DOT), such patients should be placed on DOT.

7) Adjust weight-based doses as weight changes.

8) For patients with drug susceptible pulmonary tuberculosis, treatment should be extended from 6 months to 9 months for

patients who have cavitary disease on their initial CXR *and* a positive sputum culture after 2 months of therapy.

9) A treatment algorithm for TB is shown in Figure 1, on page. 42.

B. Standard Daily Therapy for Current (Active) Disease

All patients should initially be started on a 4-drug regimen (INH, RIF, PZA, EMB) unless there are contraindications to any of the drugs or the patient is pregnant (pregnant patients may be started on a 3- or 4-drug regimen based on certain circumstances which are discussed further on page 93). See Tables 10 and Tables 11- 14 on pages 47-52 for dosing recommendations for adults and children.

Treatment regimens are listed in Table 8, page 40. Therapy for active TB disease consists of an **initiation phase** and a **continuation phase**.

The **initiation phase** generally consists of a 4-drug regimen given daily or 5 times per week per DOT. An option for twice weekly therapy after the initial 2 weeks of daily therapy ("Denver regimen") also exists: this option **should NOT be used** for patients with HIV infection, cavitary pulmonary TB, disseminated TB, vertebral TB or for patients who have co-morbid medical conditions such as diabetes mellitus, end-stage renal disease or liver disease. An intermittent regimen should NEVER be used in the initiation phase for the treatment if patients with HIV infection.

The initiation phase is followed by a **continuation phase**. For drug susceptible disease, this can consist of daily, 5 times per week, thrice weekly or twice weekly therapy by DOT (see Table 8). For

patients with HIV co-infection, in the continuation phase, twice weekly therapy is contraindicated because of increased risk of relapse with rifampin-resistant disease; in such cases therapy should be given daily (or 5 times per week) or thrice weekly by DOT. See Figure 1, page 42.

Table 8. Recommended Regimens for Treatment of Adults and Children with Drug-Susceptible Pulmonary TB

Option	Total Duration (Months)	Initial Phase		Continuation Phase		Comments
		Drugs	Interval & Dose # (minimal duration)	Drugs	Interval & Dose # (minimal duration)	
1	6^	Isoniazid Rifampin Pyrazinamide Ethambutol	Daily DOT for 40 doses (8 wks)	Isoniazid Rifampin Isoniazid Rifampin Isoniazid Rifampin Isoniazid Rifapentine	1a. Daily DOT for 90 doses (18 wks) OR 1b. Twice-weekly DOT for 36 doses (18 wks) OR 1c. Thrice-weekly DOT for 54 doses (18wks) OR 1d. Once weekly for 18 doses (18 wks)	Regimen must be, directly observed. Continue ethambutol (EMB) until susceptibility to isoniazid (INH) and rifampin (RIF) is demonstrated.
2*	6	Isoniazid Rifampin Pyrazinamide Ethambutol	Daily DOT for 10 doses (2 wks), then twice-weekly DOT for 12 doses (6 wks)	Isoniazid Rifampin Isoniazid Rifapentine	2a. Twice-weekly DOT for 36 doses (18 wks) OR 2b. Once weekly for 18 doses (18 wks)	Regimen must be directly observed. Include EMB in the initial phase. After the initial phase, continue EMB until susceptibility to INH and RIF is demonstrated. Do NOT use this regimen for HIV-infected patients*

NOTE: Daily DOT = 5 days/week (Monday through Friday). Self-administered doses (including those on weekends) will not be counted toward the total doses.

NOTE: Pyridoxine (Vitamin B_6) 25- 50 mg/daily should be added to all regimens to prevent the development of INH-induced peripheral neuropathy.

^NOTE: Duration of therapy should be extended to 9 months (31 weeks continuation phase, 39 weeks total) for patients who have cavitary pulmonary TB and remain sputum culture positive after 2 months of therapy. Some experts would extend therapy to 9 months for all patients with HIV/TB, especially those slow to convert to negative cultures or not on effective HIV treatment.

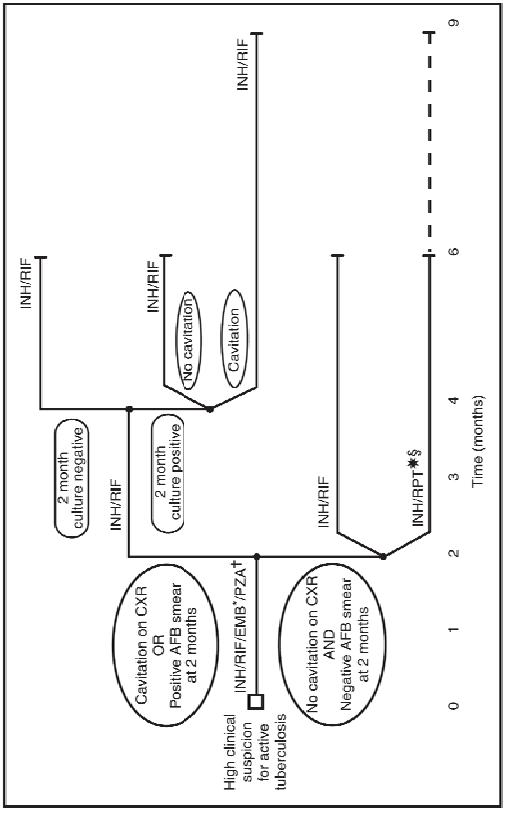
*NOTE: Option 2 should NOT be used for patients with HIV infection, cavitary pulmonary TB, disseminated TB, vertebral TB or for patients who have co-morbid medical conditions such as diabetes mellitus, end-stage renal disease or liver disease.

NOTE: Options 1d and 2b should be used only in HIV-seronegative adult patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on the initial chest radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

NOTE: Split dosing should be avoided.

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interaction

Figure 1. Treatment Algorithm for tuberculosis



Patients in whom tuberculosis is proven or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide, and ethambutol for the initial 2 months. A repeat smear and culture should be performed when 2 months of treatment has been completed. If cavities were seen on the initial chest radiograph or the acid-fast smear is positive at completion of 2 months of treatment, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment. If cavitation was present on the initial chest radiograph and the culture at the time of completions of 2 months of therapy is positive, the continuation phase should be lengthened to 7 months (total of 9 months treatment). If the patient has HIV infection and the CD4+ cell count is <100/µl, the continuation phase should consist of daily or three times weekly isoniazid and rifampin. In HIV-uninfected patients having no cavitation on chest radiograph and negative acid-fast smears at completion of 2 months of treatment, the continuation phase may consist of either once weekly isoniazid and rifapentine, or daily or twice weekly isoniazid and rifampin, to complete a total of 6 months (bottom). Patients receiving isoniazid and rifapentine, and whose 2-month cultures are positive, should have treatment extended by an additional 3 months (total of 9 months).

* EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance
† PZA may be discontinued after it has been taken for 2 months (56 doses).
❁ RPT should not be used in HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis.
§ Therapy should be extended to 9 months if 2-month culture is positive.
CXR = chest radiograph; EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine

C. Therapy for Patients with Active TB Disease with Drug Resistance or Drug Intolerance

The following medications should only be used in consultation with a physician with expertise in the management of drug-resistant TB.

Table 9. Second-Line Medications

Drug	Daily Dose	[MAX]
Streptomycin (SM): IM	**A**:15 mg/kg	[1gm]
Levofloxin: PO/IV	**C**: Consult expert **A**:750-1000 mg†	
Moxifloxacin: PO	**A**:400 mg	
Amikacin: IV, IM, Kanamycin (KM) IV/IM	**C**:15-30 mg/kg/d **A**: 15 mg/kg/d	
Capreomycin (CM): IM/IV	**C**:15-30 mg/kg **A**:15 mg/kg	[1gm]
Ethionamide: PO	**C**:15-20 mg/kg **A**:500-1000 mg	[1gm]
Cycloserine (CS): PO	**C**:15-20 mg/kg **A**:250-1000 mg	[1gm]
Para-amino-salicylic acid (PAS): PO	**C**:200-300 mg/kg **A**:150 mg/kg	[10 gm]
Clofazimine: PO	**C**:50-200 mg **A**:100-300 mg	
Bedaquiline: PO with food	**C**:Not recommended **A**:400 mg daily for 2 weeks, then 200mg thrice weekly[1]	

C= Children; A =Adults; * First line medication; can be substituted for EMB in initial regimen; † For the treatment of MDR-TB some recommend 1000mg, consult an expert for the management of MDR-TB.

Adverse Reactions
Ototoxicity (hearing loss, vestibular dysfunction); renal toxicity
GI upset; dizziness; hypersensitivity; headaches Contraindicated in children
Auditory, vestibular & renal toxicity
Auditory, vestibular & renal toxicity; hypokolemia; hypomagnesemia; eosinophilia
GI upset; hepatotoxicity; hypothyroidism; metallic taste; Bloating
Psychosis; seizures; headache; depression; other CNS effects (give 50 mg Vitamin B_6/250mg of CS)
GI upset; hypersensitivity; hepatotoxicity; sodium load; drug interactions
Orange/brown skin discoloration; GI complaints
Nausea, arthralgia, headache †

American Academy of Pediatrics. Red Book: 2012 Report of the Committee on Infectious Diseases. 29th ed. ed. Elk Grove Village, IL: Pickering LK.
[1]WHO 2013 Interim Policy Guidance; †Package insert, available at: http://www.who.int/tb/challenges/mdr/Package_insert_bedaquiline.pdf

Note: In the treatment of drug resistant disease, always use at least 3 drugs to which the organism is likely to be susceptible. **Never add a single drug to a failing regimen.** Intermittent dosing of second-line medications is not recommended.

D. Dose Counting

Although TB treatment regimens are generally described in terms of "months" of treatment, it is important that each patient receives an adequate number of doses. Thus, treatment completion is defined by number of doses actually taken as well as duration of treatment. The number of doses required for each regimen is listed in Table 8, page 40.

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Table 10. First-Line TB Drugs: Dosing for Adults (ages 15 and over) -Directly Observed Therapy (DOT) is mandatory

Drugs	Adult Dose based on body weight in kilograms (kg)*			Adverse Reactions
	Daily	Twice-Weekly	Thrice-Weekly	
Isoniazid (INH)	300 mg (5 mg/kg Maximum Dose 300 mg)	900 mg (15 mg/kg Maximum Dose 900 mg)	900 mg (15 mg/kg Maximum Dose 900 mg)	**Gastrointestinal (GI) upset** **Liver** enzyme elevation Hepatitis Peripheral neuropathy Mild effects on central nervous system Drug interactions
Rifampin (RIF)	600 mg (10 mg/kg Maximum Dose 600 mg)	600 mg (10 mg/kg Maximum Dose 600 mg)	600 mg (10 mg/kg Maximum Dose 600 mg)	**Orange discoloration of body fluids and secretions** **Drug interactions** **GI upset** Hepatitis Bleeding
Rifabutin	300 mg (5 mg/kg Maximum Dose 300 mg)	300 mg (5 mg/kg Maximum Dose 300 mg)	300 mg (5 mg/kg Maximum Dose 300 mg)	

Rifapentine	Dosed weekly in regimens 1d and 2c (Table 8) 600 mg (10mg/kg maximum dose 600 mg)			problems Influenza-like symptoms Rash Uveitis (rifabutin only)
Pyrazinamide**	40-55 kg:1000 mg 56-75 kg:1500 mg ≥76 kg:2000 mg	40-55 kg:2000 mg 56-75 kg:3000 mg ≥76 kg:4000 mg	40-55 kg:1500 mg 56-75 kg:2500 mg ≥76 kg:3000 mg	**GI upset** **Joint aches** Hepatitis Rash Hyperuricemia Gout (rare)
Ethambutol**	40-55 kg: 800 mg 56-75 kg: 1200 mg ≥76 kg: 1600 mg	40-55 kg: 2000 mg 56-75 kg: 2800 mg ≥76 kg: 4000 mg	40-55 kg: 1200 mg 56-75 kg: 2000 mg ≥76 kg: 2400 mg	Optic neuritis

*Formula used to convert pounds to kilograms: Divide pounds by 2.2 to get kilograms.
Example: Patient weighs 154 pounds ÷ 2.2 = 70 kilograms.

** Calculate **pyrazinamide and ethambutol doses using actual** body weight. **Pyrazinamide and ethambutol dosage adjustment is needed in patients with estimated creatinine clearance less than 50 ml/min or those with end-stage renal disease on dialysis.**

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interactions.

Table 11. PEDIATRIC DOSAGE - ISONIAZID IN CHILDREN (birth to 14 years)

Child's Weight in lbs	Child's Weight In kg	Daily Dose (mg) 10-15 mg/kg PO	Twice-weekly Dose (mg) 20-30 mg/kg PO
6 - 10	3 - 4.5	50	100 mg PO
11 - 14	5.0 - 6.0	50	150 mg PO
14.5 - 18	6.5 - 8.0	100	200 mg PO
18.5 - 21.5	8.5 - 9.5	100	250 mg PO
22 - 24	10.0 - 11	150	300 mg PO
25 - 29	11.5 - 13	150	350 mg PO
29.5 - 32	13.5 - 14.5	200	400 mg PO
33 - 35	15 - 16	200	450 mg PO
36 - 40	16.5 - 18.	250	500 mg PO
40.5 - 43	18.5 - 19.5	250	550 mg PO
44 - 48	20 - 21.5	300	600 mg PO
48.5 - 51	22 - 23	300	650 mg PO
52 - 54.5	23.5 - 24.5	300	700 mg PO
55 - 57.5	25 - 26	300	750 mg PO
58 - 62	26.5 - 28	300	800 mg PO
62.5 - 65	28.5 - 29.5	300	850 mg PO
≥66	≥30	300	900 mg PO

NOTE: Isoniazid tablets are available in 50 mg, 100 mg, 300 mg sizes and can be crushed for oral administration. Isoniazid tablets are also scored. Isoniazid Syrup (50mg/5ml) should not be refrigerated. It contains sorbitol and may cause diarrhea. The isoniazid syrup should only be used when crushed tablets cannot accommodate the situation (keep at room temperature).

Table 12. PEDIATRIC DOSAGES - RIFAMPIN IN CHILDREN (birth to 14 years) - DOSE for either daily or twice weekly therapy

Child's Weight in lbs	Child's Weight in kg	Dose (mg) 10-20 mg/kg
15 – 32	7 - 14.5	150
33 - 48.5	15 - 22	300
49 – 65	22.5 - 29.5	450
≥66	≥30	600

Table 13. PEDIATRIC DOSAGES - ETHAMBUTOL IN CHILDREN (birth to 14 years) - Ethambutol is available in 100mg and 400 mg tablets

Child's Weight in lbs	Child's Weight in kg	Daily Dose (mg) 15-25 mg/kg
11 – 15	5 - 7	100 mg
16 – 31	8 - 14	200 mg
32 – 44	15 - 20	300 mg
45 - 55	21 - 25	400 mg
56 – 67	26 - 30.5	500 mg
68 – 76	31 - 34.5	600 mg
77 – 87	35 - 39.5	700 mg
88 – 121	40 - 55	800 mg
122 -165	56 - 75	1200 mg
≥166	≥76	1600 mg

Table 14: PEDIATRIC DOSAGES PYRAZINAMIDE IN CHILDREN (birth to 14 years) - Pyrazinamide is available in 500 mg tablets which are scored and can be cut in ½.

Child's Weight in lbs	Child's Weight in kg	Daily Dose (mg) 30-40 mg/kg	Twice Weekly Dose (mg) 50-70 mg/kg
13 - 23	6 - 10.5	250 mg	500 mg
24 - 26	11 - 12	250 mg	750 mg
27 - 31	12.5 - 14	500 mg	1000 mg
32 - 41	14.5 - 18.5	500 mg	1250 mg
42 - 47	19.0 - 21.5	750 mg	1250 mg
48 - 54	22.0 - 24.5	750 mg	1500 mg
55 - 63	25 - 28.5	1000 mg	1750 mg
64 - 67	29 - 30.5	1000 mg	2000 mg
68 - 80	31 - 36.5	1250 mg	2000 mg
81 - 93	37 - 42.5	1500 mg	2000 mg
94 - 106	43 - 48.5	1750 mg	2000 mg
≥107 +	≥49	2000 mg	2000 mg

E. Regimen Options for the Preferred Initial Treatment of Children and Adults with Tuberculosis

1) **Initiate therapy with a 4-drug regimen as shown in Table 8.** For each of the options shown, a TB medical expert should be consulted if the patient is symptomatic or is AFB smear or culture positive after two months.

2) For patients with pulmonary tuberculosis, sputum specimens should be obtained at least on a monthly basis until two consecutive specimens are culture negative (some obtain monthly specimens throughout the course of therapy).

3) For pulmonary TB, obtaining sputum for AFB culture at the time of completion of the initial phase (e.g., 2 months) is critical and emphasized in order to identify patients at risk for relapse.

4) Extended treatment (for 3 additional months for a total of 9 months) is recommended for patients with drug-susceptible pulmonary TB who have cavitary disease on their initial CXR and a positive sputum culture after 2 months of therapy.

5) Twice-weekly therapy in the continuation phase is contraindicated for patients with HIV infection who have low CD4 counts (<100 cell/µl). We do not recommend this regimen for persons living with HIV, immunocompromising conditions, or for those with extrapulmonary or disseminated TB.

6) Newer rifamycins, rifabutin and rifapentine should be considered first-line drugs and can be used in place of rifampin in special situations: rifabutin for patients who are receiving medications, especially antiretroviral drugs that have unacceptable interactions

with rifampin; and rifapentine along with INH in highly selected patients who meet specified criteria in a once-a-week continuation phase.

Rifapentine (RPT): May be used as a primary drug in combination with INH in a once-weekly continuation phase for highly-selected patients (i.e., HIV seronegative adults, non-cavitary TB) as noted in Table 8. This regimen should NOT be used in HIV-seropositive patients or children. The weekly dose of rifapentine is 10 mg/kg per week [600 mg maximum] plus INH 15 mg/kg per week [900 mg maximum].

7) Routine follow-up is generally not needed after completion of therapy for patients who have had a satisfactory and prompt bacteriologic response and who have completed a 6 or 9 months of an INH- and RIF-containing regimen. Patients should be informed to seek prompt medical evaluation if symptoms reappear. Many authorities would continue to follow patients who are HIV-infected or who had drug resistant isolates.

Precautions

- Daily intake of alcohol increases the risk of hepatitis for patients taking INH.
- The reliability of oral contraceptives is affected in patients being treated with RIF. Alternate contraceptive measures should be recommended.
- RIF will decrease the activity of methadone and a number of other drugs (e.g., coumadin, anticonvulsants, fluconazole, protease inhibitors). An increase in methadone (often 50% more) is needed to prevent drug withdrawal. Dosage adjustment of the

interacting drugs is recommended.

- Carefully monitor renal function in patients receiving streptomycin (SM), amikacin, kanamycin, or capreomycin.
- In persons > 60 years of age, the daily dose of SM should be limited to 10 mg/kg (max dose = 750 mg).
- Never add a single drug to a failing regimen.
- **Directly observed therapy (DOT) is the standard of care for administering treatment of active TB and such treatment should be supervised and coordinated by the local health department.** For any patient on self-administered therapy, dispense only a 1-month supply of medicine at a time.

F. Drug Resistance

1. **Seek expert consultation for all patients with suspected or proven drug-resistant TB.** Treatment of TB caused by drug-resistant organisms should be done by or in close consultation with an expert in the management of these difficult situations. Second line regimens often represent the patient's last best hope for being cured. Inappropriate management can have life threatening consequences.

2. **Directly observed therapy is the standard of care for all patients with drug-resistant TB.**

3. For treatment of suspected or confirmed drug resistant TB, select at least three and if possible 4-5 drugs, to which the patient has never been exposed and to which the organism is known or likely to be susceptible. With suspected or proven MDR-TB, regimens which include 4 to 6 drugs are

recommended. **A single drug should *never* be added to a failing regimen or to one which has failed in the past.**

Table 15 provides suggestions for potential regimens for the treatment of drug resistant TB:

- For patients with only **INH resistance**, treat with RIF, PZA, EMB for a minimum of 6 months. A fluoroquinolone is sometimes added for extensive disease or in patients who cannot tolerate PZA. If used, susceptibility to the fluoroquinolone should be confirmed by drug susceptibility testing.
- For patients with only RIF resistance, treat with INH, EMB, a fluoroquinolone and PZA for a minimum of 9-12 months. An injectable agent (e.g., amikacin, kanamycin, streptomycin or capreomycin) may be included for the first 2 months of treatment for patients with extensive disease. An all oral regimen should be given for 12 months.
- MDR-TB (i.e., resistance to at least INH *and* RIF) presents difficult treatment problems. Treatment must be individualized and prolonged, based on medication history and drug susceptibility results; **seek expert consultation**. Regimens are often 24 months in duration (at least 12 months after culture conversion is documented). Surgery may be beneficial in selected patients and improve cure rates for MDR-TB patients if the bulk of the disease can be resected.

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Table 15. Potential regimens for the management

Pattern of drug resistance	Suggested regimen	Duration of treatment (mo)
INH (± SM)	RIF, PZA, EMB (a FQN may strengthen the regimen for patients with extensive disease)	6
RIF	INH, EMB, FQN, PZA (an injectable agent (IA) may be included for the first 2 months for patients with more extensive disease and/or to shorten duration, an injectable agent (Rating BIII). An all oral regimen for 12 mo should be effective (Rating BIII)	9-12
INH, RIF (± SM), and EMB or PZA	FQN, (PZA and EMB if active), IA (amikacin, kanamycin or capreomycin), and at least 2 alternative agents (e.g., ethionamide plus PAS or cycloserine); bedaquiline (TMC207) has been FDA approved, but its use requires collaboration with an expert in the field of MDR-TB*	24

Definition of abbreviations: BMRC = British Medical Research Council; EMB = ethambutol; FQN = fluoroquinolone; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; SM = streptomycin. FQN = Fluoroquinolone; most experience involves ofloxacin, levofloxacin, or ciprofloxacin. Adapted from: MMWR 2003;52(RR-11):1-77

of drug resistant tuberculosis.

Comments
In BMRC trials, 6-mo regimens have yielded ≥95% success rates despite resistance to INH if four drugs were used in the initial phase and RIF plus EMB or SM was used throughout. Additional studies suggested that results were best if PZA was also used throughout the 6 mo. Fluoroquinolones were not employed in BMRC studies, but may strengthen the regimen for patients with more extensive disease. INH should be stopped in cases of INH resistance (see text for discussion).
Daily and three times weekly regimens of INH, PZA, and SM given for 9 mo. were effective in a BMRC trial. However, extended use of an injectable agent may not be feasible. It is not known if EMB would be as effective as SM in these regimens. An all-oral regimen for 12–18 mo. should be effective. But for more extensive disease and/or to shorten duration (e.g., to 12 months), an injectable agent maybe added in the initial 2 mo. of therapy.
Use the first-line agents to which there is susceptibility. Add two or more alternative agents in case of extensive disease. Surgery should be considered (see text).

IA = Injectable agent; may include aminoglycosides (streptomycin, amikacin, or kanamycin) or the polypeptide capreomycin. Alternative agents = Ethionamide, cycloserine, p-aminosalicylic acid, clarithromycin, amoxicillin-clavulanate (Adapted from: MMWR 2003;52:1-77) or linezolid, bedaquiline (WHO, 2013 Interim Policy Guidance & Package Insert).

Table 16. ANTITUBERCULOSIS ANTIBIOTICS IN

Note: Drug adjustments are based on the patient's creatinine clearance which can be estimated as follows:

(140-age) (Ideal body weight in kg) for men (x 0.85 for women)
(72) (serum creatinine, mg/dL)

Drug	Usual Dose (UD) Normal Renal Function	CrCl 25-50
INH	300 mg/day	UD
Rifampin	600 mg/d	UD
Ethambutol	15-25 mg/kg/d	15mg/kg/d
Pyrazinamide	25 mg/kg/d (max 2.0 gm/d)	UD
Levofloxacin	750 mg/d	500 mg/d
Moxifloxacin	400 mg/d	UD
Ofloxacin	400 mg BID	400 mg/d

UD = usual dose
HD = hemodialysis
PD = peritoneal dialysis
CrCl = creatinine clearance (ml/min)
d = day

*All four first-line drugs (INH, RIF, PZA, EMB) may be administered thrice weekly after HD to facilitate DOT

ADULT PATIENTS WITH RENAL IMPAIRMENT

Ideal body weight for men: 50 kg + 2.3 kg per inch over 5 feet

Ideal body weight for women: 45.5 kg + 2.3 kg per inch over 5 feet

CrCl 10-25	CrCl <10	Hemodialysis*	Peritoneal Dialysis
UD	UD	UD	UD
UD	UD	UD	UD
15 mg/kg q 36°	15 mg/kg q 48°	15-25 mg/kg thrice weekly	15-25 mg/kg thrice weekly
20 mg/kg/d	25 mg/kg thrice weekly	25-30 mg/kg thrice weekly after HD	25 mg/kg thrice weekly
250 mg/d	250 mg/d	250 mg/d	250 mg/d
UD	UD	UD	UD
400 mg/d	300 mg/d	200mg BID	200mg/d

G. Monitoring patients on therapy

1) Response to Treatment

a. For patients with pulmonary TB, obtain sputum for AFB smear and culture at least monthly until two consecutive sputum samples are culture negative. Some authorities prefer to obtain monthly AFB sputum smear and cultures throughout the course of therapy.

b. As discussed above, it is essential to obtain a sputum culture after two months of therapy to assess risk of relapse.

c. After two months of therapy, if cultures remain or convert to positive or if symptoms do not resolve, obtain new specimens for culture and drug susceptibility testing. Such patients should be reviewed for drug resistant disease and failure to adhere to the prescribed treatment regimen. For patients receiving self-administered therapy, if cultures do not convert to negative after two months of therapy, DOT should be initiated.

d. For patients with drug susceptible TB disease who are culture positive after 2 months of therapy and have cavitary pulmonary disease on their initial CXR, the continuation phase should be increased to 7 months so that they receive a total of 9 months of therapy.

e. Factors to be considered in deciding whether to prolong treatment in patients with either cavitation on initial CXR or a positive culture after 2 months of therapy (but not both) include being more than 10% underweight at diagnosis, having HIV infection or having extensive

involvement on CXR.

f. HIV testing should be offered to all persons diagnosed with TB.

g. Given the association between TB and diabetes mellitus the point of care hemoglobin A1c test (which was recently endorsed by the American Diabetes Association) should also be considered for persons diagnosed with active TB.

2) Monitoring for Adverse Reactions

a. Obtain the following baseline measurements to detect any abnormality that would complicate the regimen or necessitate its modification:
   - Hepatic enzyme (e.g., AST or ALT) level, bilirubin, serum creatinine, complete blood count, platelet count and uric acid level (if PZA is used).
   - Baseline visual acuity (if EMB is used)
   - Baseline audiometry (if SM is used).
   - CD4 count for patients with HIV infection.

b. Patients with epidemiologic risk factors for hepatitis B or C (e.g., injection drug use, birth in Asia or Africa, HIV infection) should have serologic tests for these viruses performed.

c. All patients should be seen at least monthly while on therapy and questioned about potential adverse reactions. If symptoms suggesting drug toxicity occur, appropriate laboratory testing should be performed to confirm or exclude such toxicity. Patients should be instructed to report symptoms of hepatitis (which can be induced by

INH, RIF and/or PZA) immediately. Such symptoms include nausea, loss of appetite, vomiting, jaundice (dark urine, yellow skin), malaise, unexplained fever for $\geq$ 3 days, or abdominal tenderness. If patients have jaundice or symptoms of liver disease, discontinue medications immediately and consult a specialist.

d. Routine monthly laboratory monitoring is generally not required for those being treated for tuberculosis with normal baseline and no underlying liver disease. Monitor hepatic enzymes (ALT or AST) monthly if baseline levels are elevated, and for those with HIV infection, history of alcoholism, chronic liver disease, concomitant use of other drugs which can cause hepatotoxicity, or pregnancy. At least 20% of patients will have elevated hepatic enzymes; asymptomatic elevation less than five times the upper limit of normal is <u>not</u> an indication to stop treatment in asymptomatic patients. If patients have jaundice or symptomatic liver disease, discontinue medications immediately and consult a specialist.

e. Patients receiving EMB should be questioned regarding visual disturbances at monthly intervals; monthly repeat testing of visual acuity and color vision is recommended for patients receiving an EMB dose exceeding 15-20 mg/kg (recommended range) and for patients receiving EMB for more than two months.

f. Monitoring tests are frequently required for patients on second line drugs (based on the particular drugs being

used).

g. Pyridoxine will usually prevent INH-induced neurotoxicity (peripheral neuropathy).

h. Hyperuricemia may occur in patients on PZA but acute gout is uncommon. Asymptomatic hyperuricemia is not an indication for discontinuing the drug.

i. Drug Interactions:

- INH and phenytoin (Dilantin) increase the serum concentrations of both drugs. Follow phenytoin levels closely.
- RIF is a potent inducer of both the hepatic and intestinal cytochrome P-450 (CYP) enzyme system and P-glycoprotein (P-gp) transport system, which results in numerous clinically significant drug interactions. RIF accelerates clearance of a number of drugs metabolized by the liver including methadone, coumadin, glucocorticoids, estrogens, oral hypoglycemic agents, anticonvulsants, fluconazole, voriconazole, itraconazole, cyclosporin, and protease inhibitors.
- Women taking RIF should use a birth control method other than oral contraceptives or contraceptive implant (e.g., Norplant).

H. TB and HIV

If a patient is infected with *M. tuberculosis*, HIV infection is a very important risk factor for progression to and development of active TB disease. TB is one of the few diseases occurring in HIV-infected persons that is transmissible, curable and preventable.

Persons with HIV infection may have diminished (or absent) tuberculin skin test reactions because of immunosuppression. Therefore, tuberculin reactions of $\geq$ 5 mm of induration are considered indicative of TB infection in an HIV-infected individual (see page 8).

Because HIV status is a critical factor in the treatment of TB, **HIV counseling and testing should be offered to all patients with active TB disease.**

The clinical presentation of TB in an HIV-infected person, especially those with low CD4 count, may differ from that in persons with relatively intact cellular immunity who develop reactivation TB. Apical pulmonary disease with cavitation, a classic finding in immunologically competent persons, is less common among HIV+ persons, especially among those with low CD4 counts. HIV-infected patients may present with infiltrates in any lung zone and/or with mediastinal or hilar lymphadenopathy. Extrapulmonary and disseminated TB are common among HIV-infected TB patients.

1) Treatment for Individuals with TB & HIV

The treatment of TB in persons with HIV infection is similar to

that for patients without HIV infection. There are two important exceptions: 1) Once weekly INH-rifapentine in the continuation phase should NOT be used in any HIV-infected patient; and 2) twice weekly INH-RIF or INH-rifabutin should NOT be used for HIV-infected patients with CD4 counts <100/µl. In addition, antiretroviral therapy improves outcome among patients with TB disease who have HIV co-infection and should be initiated as discussed below.

2) HIV-infected patients with active TB disease should be initiated on a 4-drug treatment regimen (INH, RIF [or Rifabutin], PZA and EMB) and pyridoxine as outlined in Table 8 on page 40, unless contraindications to medication exist. The use of antiretroviral therapy and TB medications is discussed on pages 83-88. HIV-infected patients with drug-susceptible TB disease generally respond well to standard anti-TB drugs.

3) Patients with HIV co-infection who have drug-susceptible TB disease should be treated for a minimum of 6 months with anti-tuberculosis therapy. **Duration of therapy should be prolonged for patients with delayed or slow response to therapy.** HIV infected patients with TB disease should be monitored closely for clinical and bacteriological response. Prolonged treatment beyond 6 months (e.g., to 9 months) is recommended for patients who are slow to respond to therapy, including patients who remain culture positive after two months of therapy. Because patient adherence to therapy is crucial for good outcomes, DOT is the standard of care and is strongly recommended for all HIV-infected patients with active

TB.

4) HIV-infected patients should be monitored very closely during therapy as they appear to have a greater frequency of adverse reactions to anti-TB drugs. (Obtain a monthly AST or ALT.)

5) For patients with drug-resistant disease, if both INH and RIF are not included in the regimen, treatment should be continued for at least 18 months *and* at least 12 months after culture conversion. Directly observed therapy is essential for all patients with MDR-TB. **Seek expert medical advice** for all patients with MDR-TB.

6) After treatment is completed, patients should be reminded that if symptoms reappear, they should seek prompt medical evaluation.

I. Antiretroviral Therapy (ART) and Treatment of HIV Seropositive Patients with Active Tuberculosis Disease.

Treatment of HIV-infected patients with active TB disease should be carried out in consultation with a physician who has experience in the use of rifamycin drugs and antiretroviral agents. Recommendations on the treatment of TB in combination with antiretroviral therapy continue to evolve and it is important to check for updated guidelines.
(http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/27/)

Antiretroviral therapy (ART) improves outcomes for HIV-infected patients and decreases HIV-related mortality, including those with

TB disease. Patients in the United States with tuberculosis disease who are HIV-infected should receive treatment for HIV with ART.

Timing of ART: Several recent studies have demonstrated the benefit from early initiation of ART in patients with HIV-TB. Patients with TB/HIV had improved survival if ART was started during TB therapy rather than at the time of completion of TB therapy. Furthermore, those with TB disease and advanced HIV/AIDS with CD4 counts < 50 cells/μl^3 had improved outcomes and survival if ART was started at 2 weeks after initiation of TB therapy compared to those who were started on ART at 8 weeks.

Table 17. When to Start HIV therapy

HHS Panel Recommendations on treatment of Tuberculosis Disease with HIV co-infection: Timing of Antiretroviral Therapy (ART) Initiation relative to TB treatment	
CD4 count and/or clinical status at time of TB diagnosis	ART initiation
• < 50 cells/mm3	• within 2 weeks of starting TB therapy.
• ≥ 50 cells/mm3 with severe clinical disease**	• within 2 to 4 weeks of starting TB therapy
• ≥ 50 cells/mm3 without severe clinical disease**	• within 8 to 12 weeks of starting TB therapy
• Pregnant, any CD4 count	• As early as feasible
• MDR or XDR TB, any CD4 count	• Within 2 to 4 weeks of confirmation of drug resistance and start of second line TB therapy

** severe clinical disease: low Karnofsky score, low body mass index, low hemoglobin, low albumin, organ system dysfunction, or disseminated/widespread TB disease

Above based on guidelines developed by the Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents, last reviewed and updated March 27, 2012 (http://aidsinfo.nih.gov/guidelines).

Current recommendations are to begin ART at 2 weeks after TB diagnosis and initiation of TB therapy for those people living with HIV with CD4 counts < 50 cells/μl^3 (with the exception of those that have TB meningitis) and at 8 weeks after initiation of TB therapy for all other patients with active TB disease who have HIV co-infection.

The use of ART among HIV-TB patients is complicated by overlapping toxicity profiles of some antituberculosis and antiretroviral drugs; complex drug-drug interactions; and the occurrence of paradoxical or immune reconstitution reactions (termed immune reconstitution inflammatory syndrome [IRIS]). Additionally, a study of HIV-TB patients with meningitis found that early ART was associated with an increase in severe adverse events and no mortality benefit. Thus, timing of ART initiation in HIV-TB patients should take into account both the degree of immune suppression and site of disease (see Table 17 for specific recommendations).

Choice of ART: Because of the potential for significant drug interactions and overlapping toxicities, the choice of ART in HIV-TB patients should be made only after direct communication between HIV and tuberculosis care providers. Any change in either the TB medications or the ART regimen should be immediately shared between the 2 providers.

There are clinically important drug-drug interactions between the rifamycins (e.g., rifampin, rifabutin) and some of the antiretroviral drugs, especially protease inhibitors. The rifamycins are inducers of the cytochrome P450-3A (CYP3A) system in the liver and thereby

decrease serum concentrations of drugs metabolized by this system including protease inhibitors. Rifampin is a potent inducer of the CYP3A while rifabutin is a less potent inducer. Rifampin cannot be given with most protease inhibitors because it results in low serum levels of these drugs. Rifabutin has less of an effect and therefore can be used with certain protease inhibitors as described below.

The protease inhibitors also affect rifamycin metabolism and because the rifamycin metabolism is retarded by these drugs, the dose of rifabutin needs to be reduced in order to avoid rifabutin related toxicity.

Despite these drug-drug interactions, a rifamycin (rifampin or rifabutin) should ALWAYS be included in TB regimens for HIV co-infected patients.

Rifampin can be given with the following antiretrovirals:

- ALL Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (e.g., zidovudine, lamivudine, emtricitabine, tenofovir, abacavir). There are no significant drug interactions between the NRTIs and rifampin or other rifamycins.
- SELECTED Non-nucleoside reverse transcriptase inhibitors (NNRTIs): efavirenz only (all others are contraindicated for co-administration with rifampin). Some clinicians choose to increase the dose (from 600mg to 800mg) in patients who weigh more than 60 kg but this change in dose is probably not necessary.

- Integrase inhibitor, raltegravir. The dose of raltegravir must be increased to 800 mg BID for patients on rifampin.

Rifampin should **NOT** be used with the following:

- All protease inhibitors
- Nevirapine, etravirine, rilpivarine (all NNRTIs)
- CCR5 antagonist, maraviroc.

Rifabutin can be substituted for rifampin and used with:

- Protease inhibitors: atazanavir (with ritonavir boosting), darunavir (with ritonavir boosting), fosamprenavir (with ritonavir boosting), lopinavir/ritonavir (Kaletra). When rifabutin is given in combination with protease inhibitors, the dose of rifabutin needs to be reduced as outlined in Table 19 (page 78).
- NRTIs (e.g., e.g., zidovudine, lamivudine, emtricitabine, tenofovir, abacavir,). There are no significant drug interactions between the NRTIs and rifamycins.
- SELECTED NNRTI: efavirenz; the dose of rifabutin should be increased to 450 mg daily or 600 mg thrice weekly when administered with efavirenz.

Integrase inhibitor, Raltegravir: No dose change is needed for Rifabutin or Raltegravir when used together.

Rifapentine, a long acting rifamycin, **should NOT be used in patients with HIV co-infection.** There is a high risk of developing rifampin resistance while on TB therapy for HIV-infected persons who are treated with rifapentine-based regimens.

A summary of preferred treatment options for patients with tuberculosis disease who are HIV-infected is shown in Tables 18 and 19 on pages 76 and 78. For additional information, please refer to updated U.S. DHHS guidelines (http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/27/].

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Table 18. What to start: Choice of TB therapy and Antiretroviral Therapy (ART) when treating co-infected patients

Principle: Despite drug interactions, a rifamycin (rifampin or rifabutin) should be included in TB regimens for patients receiving ART, with dosage adjustment if necessary (see Table SMR11 for dosage adjustments).
Option 1a: TB regimen: Rifampin-based Preferred ART regimen: Efavirenz (NNRTI) + 2 NRTIs (TDF/FTC or ABC/3TC) Contraindicated medications: o All PIs o Other NNRTIs: Nevaripine, Delviridine, Etravirine, or Rilpivirine
Option 1b: TB regimen: Rifampin-based ART regimen: Integrase-inhibitor (RAL) dose-adjusted + 2 NRTIs Preferred ART choices: RAL + TDF/FTC Alternative ART choices: RAL + ABC/3TC
Option 2a: TB regimen: Rifabutin (dose adjusted) substituted for Rifampin ART regimen: boosted PI + 2 NRTIs Preferred ART choices: ATV/r + TDF/FTC DRV/r + TDF/FTC Alternative ART choices: • ATV/r + ABC/3TC • DRV/r + ABC/3TC • FPV/r (once or twice daily) + ABC/3TC or TDF/FTC • LPV/r (once or twice daily) + ABC/3TC or TDF/FTC
Option 2b: TB regimen: Rifabutin substituted for Rifampin ART regimen: Integrase-inhibitor (RAL) usual dose + 2 NRTIs Preferred ART choices: RAL + TDF/FTC Alternative ART choices: RAL + ABC/3TC
Choice for Pregnant women with active TB and HIV infection: TB regimen: Rifabutin (dose adjusted) substituted for Rifampin ART regimen: LPV/r (twice daily) plus ZDV/3TC

NRTIs: nucleoside/-tide reverse transcriptase inhibitors
NNRTIs: non-nucleoside reverse transcriptase inhibitors
PIs: protease inhibitors

TDF: Tenofovir
FTC: Emtricitabine
ABC: Abacavir
3TC: Lamivudine
ZDV: Zidovudine
ATV/r: Atazanavir/ritonavir
DRV/r: Daraunavir/ritonavir
LPV/r: Lopinavir/ritonavir
FPV/r: Fosamprenavir/ritonavir
RAL: Raltegravir

Table 19. Dosage Adjustments for ART and Rifamycins when used in Combination

	Rifampin (RIF)	Rifabutin (RBT)
NNRTI		
Efavirenz (EFV)	RIF no change (600 mg) EFV: no change (600 mg qhs) *Some clinicians increase EFV to 800 mg/d for pts > 60 kg	RBT: increase to 450 mg/d or 600 mg/tiw EFV: no change (600 mg qhs)
Boosted PI		
ATV/r, DRV/r, LPV/r, FPV/r	DO NOT USE	RBT: decrease to 150 mg/d or 300 mg/tiw PIs: no change
Integrase Inhibitor		
Raltegravir (RAL)	RIF: no change (600 mg) RAL: increase to 800 mg bid	RBT: no change (300 mg) RAL: no change (400 mg bid)

NNRTIs: non-nucleoside reverse transcriptase inhibitors
PIs: protease inhibitors
ATV/r: Atazanavir/ritonavir
DRV/r: Daraunavir/ritonavir
LPV/r: Lopinavir/ritonavir
FPV/r: Fosamprenavir/ritonavir
RAL: Raltegravir

J. Paradoxical Reactions or Immune Reconstitution Inflammatory Syndrome (IRIS) Associated with Initiation of Antiretroviral Therapy During the Course of TB Therapy

The temporary exacerbation of TB symptoms and lesions after initiation of anti-tuberculosis therapy - known as a paradoxical reaction or immune reconstitution inflammatory syndrome (IRIS) - has been described as a rare occurrence in HIV-seronegative patients after the initiation of anti-tuberculosis therapy. These "paradoxical reactions" are thought to be due to immune reconstitution and are not uncommon among HIV-infected patients who are started on antiretroviral therapy (ART) early in the course of antituberculosis therapy. A recent meta-analysis reported that about 16% of patients with TB disease and HIV co-infection developed IRIS after starting ART and TB IRIS mortality was 3% (Müller et al). Overall, the benefits of early ART, especially among those with advanced HIV/AIDS outweigh the adverse effects that can be seen with IRIS.

Paradoxical reactions or IRIS are characterized by fever, worsening infiltrates on chest radiograph, new enlarging and peripheral and/or mediastinal adenopathy and cold abscesses, new or worsening CNS TB, and new or worsening serositis. The paradoxical reactions are associated with increase reactivity on tuberculin skin testing and a significant reduction in HIV viral load. Patients with clinical findings that are compatible with IRIS should have other diagnoses ruled out. These paradoxical or immune reconstitution reactions are usually self-limited and can last 10 to 40 days. Mild to moderate reactions can be managed by reassurance and non-steroidal anti-inflammatory drugs. Severe reactions included those characterized by marked

increase in adenopathy causing an anatomic problem (e.g., compromised breathing, swallowing or movement of the neck; or expanding central nervous system lesions) can be managed with corticosteroids (with continuation of the antituberculosis therapy and ART) starting at a dose of prednisone or methyl prednisolone of 1 mg/kg per day and then tapering the therapy after 1 to 2 weeks of therapy.

K. Treatment of Extrapulmonary Tuberculosis

The basic principles that underlie the treatment of pulmonary TB also apply to extrapulmonary forms of the disease. A 6-month course of therapy is recommended for treating tuberculosis involving any site with the exception of the meninges for which a 9-12 month regimen is recommended. Prolongation of therapy also should be considered for patients with tuberculosis in any site that is slow to respond. The addition of corticosteroids is recommended for patients with tuberculosis pericarditis and meningitis as it improves outcome and decreases mortality as discussed below.

Lymphatic and hematogenous TB are especially common among persons with HIV infection. Central nervous system (CNS) involvement has been reported and may be difficult to diagnose when it occurs in conjunction with other opportunistic CNS infections.

To establish the diagnosis of extrapulmonary TB, a variety of specimens including pleural fluid, peritoneal fluid, pleural and peritoneal biopsy specimens, lymph node tissue, bone marrow, bone, blood, urine, brain or cerebrospinal fluid may need to be obtained for mycobacterial culture.

Specimens must be examined microscopically and sent for AFB culture, but the inability to demonstrate AFB on smear and the absence of granuloma formation does not exclude the diagnosis of TB. Surgery may be necessary to obtain specimens for diagnosis and to treat such processes as constrictive pericarditis or spinal cord compression from Pott's disease (spinal tuberculosis). Evidence-based guidelines for the treatment of extrapulmonary TB and adjunctive use of corticosteroids are shown in Table 20 page 82.

Table 20. Evidence-based* guidelines for the treatment of extrapulmonary tuberculosis and adjunctive use of corticosteroids in patients with drug susceptible disease in adults.

Site	Length of therapy (mo)	Rating (duration)	Corticosteroids	Rating (corticosteroids)
Lymph node	6	AI	Not recommended	DIII
Bone and joint	6–9	AI	Not recommended	DIII
Pleural disease	6	AII	Not recommended	DI
Pericarditis	6	AII	Strongly recommended	AI
CNS tuberculosis including meningitis	9–12	BII	Strongly recommended	AI
Disseminated disease	6	AII	Not recommended	DIII
Genitourinary	6	AII	Not recommended	DIII
Peritoneal	6	AII	Not recommended	DIII

* For rating system, see Table 3.

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VI. Pregnancy

A. Treatment for LTBI and Risk Factors

A pregnant woman with a positive skin test (or positive IGRA test) and negative chest x-ray (a lead apron should cover the entire abdomen during x-ray) should be started on treatment for LTBI with INH (300 mg daily) *immediately* if they have one or more of the following risk factors:

- Documented recent tuberculin skin test conversion;
- HIV infection or those with HIV risk factors who refuse HIV testing;
- Close contact of patient with AFB smear-positive pulmonary TB.

Pyridoxine (25-50 mg/d) is recommended for all pregnant or nursing mothers who receive INH. All pregnant and immediate post-partum patients should have a baseline and monthly AST (or ALT) performed while on therapy. Treatment of other pregnant women with a positive diagnostic test for LTBI can be deferred until several months after the completion of pregnancy.

B. Treatment of Active TB in Pregnancy

TB disease discovered during pregnancy should be treated without delay. Because of the risk for tuberculosis to the fetus, treatment of TB in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. Two or three sputum samples should be submitted for examination. The outcome of the cultures and susceptibility test results will determine the regimen for continuation of treatment.

1) Drug Treatment in Pregnancy (See Table 21, page 86)

a) The initial treatment regimen usually consists of INH, RIF and EMB; strong consideration should be given to including PZA in the initial regimen.

b) Although detailed teratogenicity data are not available, PZA can probably be used safely during pregnancy and is recommended for use by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD). In some U.S. jurisdictions, PZA has not been routinely recommended. PZA should be included in the initial regimen for HIV-seropostive women and for HIV seronegative women who are thought to be at high risk for drug resistant TB. If PZA is not included in the initial treatment regimen, the minimum duration of therapy is 9 months.

c) Pyridoxine (Vitamin B_6) (25 mg/d) is recommended for all pregnant women taking INH.

d) ***Avoid:*** Aminoglycosides (e.g., streptomycin, kanamycin, amikacin) and capreomycin are contraindicated for all pregnant women because of potential adverse effects on the fetus. Fluoroquinolones (e.g., levofloxacin, ofloxacin, moxifloxacin, gatifloxacin, ciprofloxacin) have been associated with arthropathies in young animals; therefore, they should be avoided if possible in pregnant women. Because of lack of data, avoid ethionamide and cycloserine in pregnancy.

2) Breast Feeding

The small concentrations of first line TB drugs in breast milk do not have a toxic effect on nursing new-borns and **breast feeding should**

not be discouraged. Conversely, drugs in breast milk should not be considered to serve as effective treatment for disease or as treatment of LTBI in a nursing infant.

Table 21. Use of Anti-TB Medications in Special Situations: Pregnancy, Tuberculous Meningitis and Renal Failure

Drug	Safety in Pregnancy (1)	Central Nervous System Penetration (2)	Dosage in Renal Insufficiency (3)
Isoniazid	Safe (4)	Good (20-100%)	No change
Rifampin	Safe (isolated reports of ma-formation)	Fair, Inflamed meninges (10-20%)	No change
Pyrazinamide	Caution (1)	Good (75-100%)	Decrease dose/ Increase interval
Ethambutol	Safe	Inflamed meninges only (4-64%)	Decrease dose/ Increase interval
Aminoglycosides (Streptomycin, Kanamycin, Amikacin)	Avoid	Poor (5)	Decrease dose/ Increase interval (6)
Capreomycin	Avoid	Poor	Decrease dose/ Increase interval (6)
Levofloxacin, Moxifloxacin Gatifloxacin	Do not use	Fair (5-10%) Inflamed meninges (50-90%)	Decrease dose/ Increase interval (7)
Ethionamide	Do not use	Good (100%)	No change
Cycloserine	Avoid	Good (50-100%)	Decrease dose/ Increase interval
Para-amino-sili-cylic acid	Safe	Inflamed meninges only (50-100%)	Incomplete data
Clofazimine	Avoid	Unknown	Probably no change

Safe: Drug has not been demonstrated to have teratogenic effects.
Avoid: Limited data on safety or for aminoglycosides asssociated with hearing impairment and/or other toxicity.
Do Not Use: Associated with premature labor, congenital malformations or teratogenicity.

NOTES: Table 21: Special Situations

(1) As with all medications given during pregnancy, anti-TB drugs should be used with caution. The risk of TB to the fetus far outweighs the risk of medications. Pregnant patients with active TB should be treated. Data are limited on the safety of some anti-TB drugs during pregnancy. Table 21 presents a consensus of published data and recommendations. Although detailed teratogenic data is not available, PZA can probably be used safely for pregnant patients. Concentrations of anti-TB drugs in breast milk are low; treatment with these medications is not a contraindication to breastfeeding. (Conversely, medication present in breast milk is not sufficient to prevent or treat TB in the newborn.) Consult a medical expert when treating a pregnant patient who has TB. For treatment of LTBI, most authorities recommend beginning INH several months after delivery, unless the woman is at high risk for progression to active TB (e.g., recent TST or IGRA conversion, HIV-infected).

(2) Steroid treatment appears to improve outcome in TB meningitis, particularly in patients with altered mental status.

(3) If possible, monitor serum drug levels of patients with renal insufficiency. See pages 60-65 for dosage.

(4) Supplement with pyridoxine (Vitamin B6) during pregnancy.

(5) Has been used intrathecally; efficacy not documented.

(6) Avoid aminoglycosides and capreomycin in patients with reversible renal damage, if possible.

(7) Fluoroquinolones may accumulate in renal failure and are poorly removed by dialysis. Dose adjustment indicated.

VII. Childhood Tuberculosis

The basic principles for treatment of TB disease and infection in children and adolescents are essentially the same as adults. The objective of treatment is to kill the tuberculous bacilli in the shortest amount of time while preventing the development of resistance. Dosage adjustments of medications may often be required based on weight. When possible, crushed tablets or the mixed contents of capsules are preferred over suspensions that may be difficult to access and may contain less desirable additives.

The TST is the most commonly used test for diagnosing LTBI and tuberculosis disease in children. Immunologic-based testing (IGRA's) may be used as an alternative to TST placement in immune competent children 5 years of age and older to aid in LTBI or TB disease diagnosis. The involvement of a provider with expertise in management of children with tuberculosis infection or disease is beneficial in guiding diagnostic evaluation and treatment.

A. Management Considerations

1) TB disease in infants and children younger than 4 years of age is much more likely to disseminate; therefore, prompt evaluation and treatment should be started when the diagnosis is suspected.

2) As the yield of an organism from sputum specimens in children is rare, it may be necessary to rely on the results of cultures and susceptibility tests of specimens from the adult source case to guide the treatment regimen. In cases of suspected drug-resistant TB or when the *M. tuberculosis* isolate from the presumed source patient is not available, obtaining induced sputa or early morning gastric

aspirates may be beneficial. In certain situations, bronchoalveolar lavage or tissue biopsy may be considered.

3) Primary intrathoracic TB (parenchymal infiltration, hilar adenopathy, or both, in a child with evidence of tuberculosis exposure) should be treated in the same manner as pulmonary TB.

4) An empiric regimen of four drugs (INH, RIF, PZA, EMB) for 2 months and RIF and INH for the remaining 4 months when the possibility of drug resistance is low is recommended. A three drug regimen (INH, RIF, PZA) can be used as initial therapy when the isolate (i.e., from source TB case) is known to be fully drug susceptible. Children and adolescents with "adult-type" tuberculosis consisting of cavitation and AFB positive sputum samples should receive a 4-drug regimen initially until susceptibility is proven. The persistence of cavitary lesions and/or the detection of AFB in sputa specimens may warrant extension to a 9-month course of therapy.

When clinical or epidemiologic circumstances suggest an increased probability of INH resistance, EMB can be used safely at a dose of 15-20 mg/kg per day as a fourth drug, even in children too young for routine eye testing. Streptomycin, kanamycin or amikacin can also be used as a fourth drug when necessary and may be considered for TB meningitis.

5) In general, extrapulmonary TB, including cervical adenopathy (scrofula), can be treated with the same regimen as pulmonary TB (i.e., 6 months for drug-susceptible disease). Exceptions include TB meningitis for which 12 months of therapy is currently recommended.

6) Directly observed therapy is the standard of care for all children. HIV testing should be performed on all individuals with TB disease (including children) as the treatment regimen (including need for antiretroviral therapy) is altered with HIV infection.

7) Clinical and radiographic examinations may be monitored for response to therapy. However, resolution of abnormal findings on chest radiography with pulmonary or intrathoracic lymphadenopathy may lag behind clinical response. Chest radiography is usually not performed at the conclusion of a successful course of treatment and should not be used as a criterion for discontinuing anti-TB drugs.

8) Management of the newborn infant whose mother or other caregiver is suspected of having TB is based on individual considerations. Separation of the mother (or caregiver) and infant should be minimized, if possible. Differing circumstances and resulting recommendations are as follows:

i. *Mother or other caregiver who has a positive tuberculin skin test or IGRA and normal chest radiography.* If, after investigation, no evidence of active TB disease is found in the mother or caregiver to whom the infant is exposed, separation of mother or caregiver and infant is not indicated. These mothers may breastfeed their infants. Evaluation of all contacts should be performed to attempt to identify a source case.

ii. *Mother or other caregiver who has abnormal chest radiography suggestive of tuberculosis disease but is judged to be noninfectious at delivery.* The situation in which a mother or caregiver's history, physical examination, and sputa examination do not suggest active

disease may be considered to be a low risk exposure and the separation of mother/ caregiver and the infant is not necessary. The mother/ caregiver should receive therapy and contacts should be evaluated with a TST or IGRA to attempt to identify a source case. The infant should be followed closely by a pediatric provider.

iii. *Mother who has active TB disease and is suspected of being infectious at the time of delivery.* The infant should be assessed for evidence of congenital tuberculosis and the mother/caregiver should be evaluated for HIV infection. A healthcare provider with expertise in the treatment of infants with congenital tuberculosis should be consulted to assist with management of the infant's anti-TB regimen. If congenital tuberculosis is not suspected, the infant should receive INH (10 mg/kg/ dose) daily until the infant is 3 – 4 months of age when a TST should be placed. If the TST result is reactive, an evaluation for tuberculosis disease should be conducted. If TB disease is excluded, the infant should continue to receive INH until 9 months of age with monthly assessments to complete treatment for LTBI. If the TST at 3–4 months of age is nonreactive and the mother/ caregiver's compliance can be documented, the infant's INH may be discontinued.

The mother/caregiver and infant should be separated until the mother/caregiver and infant have received appropriate antituberculosis therapy. The mother/caregiver should wear a mask and follow appropriate infection control procedures until she/ he has been judged to be noninfectious. The mother/caregiver should be separated from the infant in situations where infection with MDR TB is possible and/or adherence to therapy cannot be documented. BCG immunization may be considered for the infant in these situations.

Women with tuberculosis disease who have received 2 weeks of appropriate therapy and who are not considered to be contagious may breastfeed. A healthcare provider with expertise in tuberculosis should be consulted to assist with recommendations in individual situations when a women receiving antituberculosis therapy wishes to provide human milk to an infant.

VIII. Tuberculosis and Long Term Care Facilities

TB remains a problem in older individuals who infected many years ago and did not develop active disease at the time. Also, there is increasing documentation of outbreaks of TB occurring in nursing home residents when a patient with TB disease infects a population of older people who are newly exposed to that case.

TB control in nursing homes and long term care facilities must begin with a careful assessment of TB status upon admission, including a diagnostic test for LTBI (TST or IGRA). For those with a positive diagnostic test for LTBI, an assessment and chest x-ray should be performed as described above to exclude active TB disease.

Since people over 50 years old may have diminished skin test reactivity, the two-step technique (see page 11) of tuberculin skin testing is recommended at admission to the nursing home if the TST is the diagnostic test being performed to screen for LTBI. A "booster effect" with the TST has been noted in elderly persons in whom the delayed type hypersensitivity (DTH) reaction to tuberculin may have waned over the years. In these situations, an initial tuberculin skin test may demonstrate a negative reaction but it boosts the immune system so that subsequent tuberculin skin tests may be increased in size and may be interpreted as positive. This "boosted" response is considered as the valid baseline for the individual and thought to represent latent TB infection (after active disease is excluded).

Residents of nursing homes or long term care facilities whose baseline two-step skin tests are negative (or whose baseline IGRA is negative if the IGRA is being used to screen for LTBI) on admission should have repeat testing performed when an exposure to a case of potentially infectious TB has occurred.

- Any person who converts a TST or IGRA from negative to positive should be considered for treatment of LTBI after active TB is ruled out (by chest x-ray at a minimum and sputum specimens if indicated).
- Any resident with symptoms of TB regardless of TST (or IGRA) results should have a chest x-ray to evaluate for active TB disease.
- Treatment of active TB disease (Class III) is the same as that used for younger adults.

Employees of nursing homes or long term care facilities should have two-step tuberculin testing when they start to work in the nursing home (if the TST is used for testing of health care workers), and annual testing thereafter (if they have not had a TST in the year prior to initiating employment). Employees who are TST (or IGRA) positive at baseline should be evaluated for treatment of LTBI (see pages 24-30). Those with recent conversion should be strongly encouraged to take treatment for LTBI. Routine annual symptom screening for previously positive TST employees is recommended instead of an annual CXR.

IX. BCG Vaccination

Bacille Calmette-Guerin (BCG) vaccine is one of the most commonly used vaccines in the world and is given in the vast majority of low and middle income countries. BCG is recommended in higher TB prevalence areas because it has a documented protective effect against TB meningitis and disseminated TB in children. It does not prevent primary infection and, more importantly, does not prevent reactivation of latent pulmonary infection, the principal source of bacillary spread in the community. The impact of BCG vaccination on transmission of *M. tuberculosis* is therefore very limited (or there is no impact). BCG has not impacted the global epidemiology of TB. Because of variable efficacy, *BCG is NOT recommended in the U.S.* BCG is not a contraindication to a TST but as noted there can be cross reactions between BCG and the TST. The primary advantage of IGRAs is that they do not cross react with BCG. Interpretation of a tuberculin skin test reaction is not changed for patients who have received BCG. A reaction of ≥10 mm (≥ 5mm in HIV-infected persons) of induration should be considered infection with *M. tuberculosis* because:

- Conversion rates after BCG vaccination are not 100%;
- The mean reaction size among BCG vaccinees is often less than 10 mm (a large reaction is more likely to be due to infection with *M. tuberculosis* than BCG vaccination);
- Tuberculin sensitivity tends to wane considerably after BCG vaccination; and,

- BCG is often given in areas where TB is endemic, so assume that the reaction is from infection, not vaccination.

Since many BCG-vaccinated persons come from areas of high TB prevalence, it is important that persons with a positive TST be evaluated for presence of TB disease and managed accordingly. Appropriate follow-up includes a careful medical history, CXR to rule out active TB disease, and evaluation for treatment of LTBI. An IGRA is the preferred LTBI test among individuals with a history of BCG vaccination but a TST is an acceptable test in BCG-vaccinated persons.

X. TB Infection Control: Hospital Isolation Procedures

Effective infection control efforts are essential in preventing nosocomial transmission of TB. A hierarchy of control measures is recommended to prevent TB transmission in health care facilities.

A. Administrative Controls

Administrative controls are most important and include measures to reduce the risk of exposure to persons with infectious TB; this includes careful screening, early identification and treatment of patients with TB. A high index of suspicion is critical. Patients with or at risk for TB need to be isolated upon admission (placed in a negative pressure airborne infection isolation [AII] room). Unsuspected patients with active TB disease and misdiagnosis (especially among HIV-infected patients who may have "atypical" or non-classical presentations) have led to nosocomial transmission at a number of hospitals (as well as at correctional institutions and other health care facilities).

Grady Memorial Hospital in Atlanta has prevented nosocomial transmission in large part by the effective use of administrative controls. Careful screening of patients and isolation of those at risk for TB have been accomplished by the introduction of an expanded respiratory isolation policy.

B. Surveillance for Health Care Workers

All health care workers should have baseline test for LTBI (unless *documented* to be previously TST positive) and at intervals determined by their risk of exposure. Two-step tuberculin skin testing upon employment is recommended unless the HCW had a TST in the prior year. For serial testing of HCWs, we recommend the use of the TST rather than an IGRA for reasons described above (Section IX). The frequency of tuberculin skin testing (or IGRA if that is used) is determined by the risk assessment. For healthcare workers in *medium risk* settings (i.e., institutions with ≥ 200 beds and 6 or more TB cases per year or < 200 beds and ≥ 3 TB cases per year), testing should be done annually. For low risk settings (i.e., ≥ 200 beds and less than 6 TB cases or < 200 beds and < 3 TB cases per year), testing of healthcare workers should be done at baseline and then only if an exposure occurs but not on a routine basis. TB clinics and TB outreach programs should be considered medium risk. Any inpatient or outpatient setting with evidence of recent patient to patient or patient to healthcare worker transmission of *M. tuberculosis* should be classified as *potential ongoing transmission* until appropriate control measures have been implemented and transmission ceases. This is a temporary classification which requires immediate interventions; healthcare workers in such settings should be tested for LTBI every 3 months until transmission has been terminated.

Any worker who develops symptoms of active TB disease or whose test for LTBI (TST or IGRA) converts to positive should be evaluated promptly. Health care workers with recent TB infection

on the basis of a conversion to a positive test for LTBI (regardless of age) and no evidence of active disease should be encouraged to take treatment for LTBI (see pages 24-34). Health care workers should be educated about the basic concepts of TB transmission and pathogenesis, infection control practices, and the signs and symptoms of TB.

Grady Hospital TB Isolation Policy

Criteria for Isolation	Length of Isolation
1. Active Pulmonary TB	Duration of hospitalization if less than 4 weeks; if >4 weeks must have clinical response, drug susceptibility data and 2 negative AFB sputum smears
2. "Rule Out" TB Any patient who has sputum for AFB collected or pulmonary TB is in the differential diagnosis.	Until 2 sputum AFB smears are negative
3. HIV+ patient admitted with abnormal CXR	Until 2 sputum AFB smears are negative

C. Environmental Controls

Patients admitted to health care facilities with suspected or confirmed TB should be placed in an airborne infection isolation (AII) room (i.e., negative pressure rooms with $\geq$ 6 air changes per hour; $\geq$ 12 for new construction); air from AII rooms should be exhausted directly to the outside or through a HEPA filter before being recirculated.

D. Personal Respiratory Protection

Appropriate respirator masks should be worn by health care workers when entering AII rooms or performing high risk procedures such as cough inductions and bronchoscopy. Use of a N-95 respirator by health care workers is the minimum level of protection required by OSHA.

XI. Community Tuberculosis Control

A. Reporting Requirements

- In Georgia, the law requires ***all TB cases must be reported to the local county public health department***. This is the responsibility of the physician. At Grady Memorial Hospital, the TB Control Coordinator in the Epidemiology Department (404-616-3598) reports all patients with active disease to the local health departments for the physician. Any health care provider who is managing TB patients in non-health department settings must update the health department on the progress of each patient, including sputum results on a quarterly basis. Cases may be reported electronically at http://sendss.state.ga.us, by calling 1-866-782-4584, or by calling your local health department.

- Addition reporting requirements

  ALL Latent TB infection (LTBI) in children under 5 years of age must be reported to the patient's local county public health department.

  A Source Case Investigation should be conducted by the health department when LTBI is found in a child under 5 years old.

B. Role of the Health Department

Health department staff are trained and experienced in contact investigation, provision of directly observed treatment of latent TB infection (LTBI) and directly observed therapy (DOT) for the treatment of patients with active disease. **DOT is the standard of care for all patients with TB disease in Georgia and is strongly recommended for all patients with tuberculosis to facilitate adherence and completion of therapy.**

Role of the Health Department

- Identify and treat all persons with TB disease; ensure that patients complete appropriate therapy
- Provide Directly Observed Therapy (DOT)
- Provide laboratory services
- Identify and evaluate contacts to persons with infectious TB; offer therapy as appropriate
- Screen high-risk groups for TB infection; offer therapy as appropriate
- Collect and analyze data
- Provide training, education, and consultation testing should be only one test.

Early reporting of suspected or confirmed TB cases is important for control of TB and it gives the clinician access to the resources of the public health department for assistance in case management and contact investigation. Contact investigations are indicated to determine those who have been exposed to infectious TB patients so tuberculin skin testing can be performed on close contacts and treatment of LTBI can be initiated for those who have been infected.

Tuberculosis services (radiology, medical consultations, DOT, etc.) are available in every health district. All TB medications are provided by the state pharmacy free of charge.

C. Grady Hospital TB Discharge Policy

For TB control efforts, it is important that there be a smooth transition from the in-patient to the out-patient setting and close cooperation and coordination of activities among the wide variety of organizations involved in TB patient care, education and TB control.

To improve TB control efforts in Atlanta and protect the community from TB, a TB Discharge Policy has been developed for Grady Memorial Hospital. The standard requires that:

- Patients be discharged on an appropriate anti-TB regimen (e.g., 4 drug regimen)
- All TB patients have their discharge endorsed in the chart *prior to discharge* by the Hospital's TB social worker and the local health department liaison;
- All TB patients meet appropriate criteria for discharge according to the following policy:

Summary:
Grady Hospital TB Discharge Policy

Site & Patient Characteristics	Criteria
I. Another Acute Care Hospital	Transfer anytime when stable
II. Prison with Appropriate Isolation	Transfer when medically ready for discharge unless MDR-TB suspected
III. American Lung Association (ALA) Alternative Housing Program (GA DPH/ALAG)	Transfer when medically ready for discharge
IV. Home	When medically ready for discharge **AND** the criteria shown in the chart on the following page are met:

Patient Characteristics	Discharge Destination	Criteria (See Below)
Known or suspected MDR-TB	Stable Home	Need A, B, C, D, H
	Unstable Home or Prison	Cannot discharge to these sites
Cavitary or moderate infiltrate and/or positive initial respiratory AFB smear	Stable Home	Need A, B, C, H
	Unstable Home	Need C, E, F, I or C, E, F, G
Minimal or no infiltrate & initial AFB respiratory smears (≥3) were negative	Stable Home	Need A, B, & C
	Unstable Home	Need C, E, & F
Non-respiratory TB closed site of infection (Pleural, etc.)	Stable Home	Need A, B, & C
	Unstable Home	Need C, E, & F
Non-respiratory TB open site of infection (skin, etc)	Stable Home	Need, A, B, C, D
	Unstable Home	Need C, D, E, & F
Positive AFB smear now; previous positive culture for non-TB Mycobacteria collected within 60 days	Stable Home	Need A, B, C, D, H
	Unstable Home	Need C, D, E, & F
Situations Other Than Those Above	Stable Home	Need A, B, C, & D
	Unstable Home	Need C, D, E, & F

Keys to Letters Defining Criteria:

A. Social service and county health department liaison have documented stable/appropriate home environment.

B. Arrangement is made and documented in the chart for follow-up visit by appropriate county health dept, clinic or other appropriate health care provider, as soon as possible and no longer than 10 week days after discharge. Patient (and/or family and/or significant other) are informed of arrangement.

C. Patient (and/or family and/or significant other) has received discharge teaching about the disease and about isolation, if appropriate.

D. Pulmonary or infectious diseases consult or hospital epidemiologist endorses in chart that disposition is appropriate.

E. Social service and the county health liaison document unstable home environment.

F. Patient has arrangement made and documented in chart for follow-up visit by county health dept, clinic or other appropriate health care provider, as soon as possible (no longer than 5 week days after discharge). Patient, family and/or significant other are informed of arrangement.

G. After 2 negative AFB smears.

H. Patient has good clinical response to initial anti-TB therapy and when medically stable: there will be no new persons exposed to the patient in the home who have not been in long-term contact with the patient prior to hospitalization; patient (and family or significant others, as applicable) agrees to and is assessed as likely to comply with isolation of the patient at home, until the patient is seen by the county health department

I. Patient accepted into American Lung Association (ALA) Alternative Housing Program.

D. The U.S.-Mexico Binational Tuberculosis Referral Program (CureTB)

CureTB (**www.curetb.org**) is part of the San Diego County Public Health Services TB Control Branch a referral and continuity of care program for tuberculosis patients and their contacts who travel between the United States and Mexico. Services are available for patients, their families and providers from any state in the United States or Mexico. CureTB also provides services for patients travelling to other countries.

CureTB facilitates and supports continuity of care for individuals with active tuberculosis disease and their contacts, and provides linkages to ongoing care and follow-up for all referred patients. CureTB accepts referrals from health departments, correctional facilities, and other entities that diagnose or treat patients with tuberculosis.

The **Binational Card** is a tool to help mobile patients and their families connect with CureTB when they arrive at their next destination. They can also give the card to their provider to connect with CureTB to obtain the latest clinical information. The card is easy to carry and has the CureTB 1-800 number, reachable from inside or outside the US.

To request binational cards

- Telephone: (619) 542-4013
- e-mail: curetb.hhsa@sdcounty.ca.gov

CureTB accepts referrals for

- Persons with active Tuberculosis and those suspected of having TB
- Contact Notification
- Source Case Finding
- Clinical History Request

To Submit a CureTB Referral

You can submit a CureTB referral in three ways. Use a **referral form** and attach hard copies of relevant clinical information whenever possible. Visit the www.curetb.org website for additional information regarding the relevant clinical information for the different types of referral.

1. **Fax:** (619) 692-8020
2. **E-mail:**curetb.hhsa@sdcounty.ca.gov
3. **Call:** (619) 542-4013

XII. Georgia Department of Public Health (DPH) Community Guidelines for Respiratory Isolation of Patients with Active TB in the Community

In setting guidelines, the Georgia Department of Public Health (DPH) follows CDC recommendations that a stepwise approach be used to seek the least intrusive policy that is consistent with maintaining the health of the community. These guidelines provide a framework for clinical management of TB patients. The management of each patient must be customized to the individual's circumstances, living environment, and compliance with TB therapy. The guidelines classify active TB cases into three grades of infectiousness and two grades of organism resistance. They recommend appropriate levels of housing options and degrees of respiratory isolation for each grade of infectiousness and resistance. Infectiousness is graded by AFB smear, TB culture results, clinical improvement in response to medical therapy, and evidence of adherence with therapy.

Grades of Infectiousness:

Grade I: smear positive, culture positive

Grade II: smear negative, culture positive or unknown

Grade III: smear negative, culture negative

Smear negative = three consecutive negative sputum AFB smears on separate days.

Culture negative = three consecutive negative AFB cultures one week apart.

Drug susceptibility or drug resistance is based on the drug susceptibility testing results on the *M. tuberculosis* isolate recovered from the patient. TB isolates are considered fully susceptible if they have been shown to be susceptible to all first line anti-TB drugs. Resistant strains are those resistant to one or more anti-TB drugs.

Housing options include home for patients who can return to a stable home and three levels of facilities for those without a stable home.

Levels of housing:

Level 1: Acute care hospital
Alternative Housing Program (smear positive, medically stable and clinical improving)

Level 2: Shelters that require negative smears; trained staff provide DOT, Alternative Housing Program (smear positive, medically stable and clinical improving)

Level 3: Shelters that require negative cultures; trained staff for DOT available

These categories of respiratory isolation, based on guidelines from the National Jewish Center for Immunology and Respiratory Disease, regulate patient activities and use of masks based on grade of infectiousness:

A) Activity defined by the Level 1 institution;
B) Home permitted provided that no new persons will be exposed in the home;
C) Wear mask to medical appointments, otherwise stay home;
D) Wear mask only when indoors around unexposed persons.

Per CDC guidelines, use simple surgical masks for patients. Isolation categories apply to patients with clinical improvement in response to medical therapy (e.g., resolution of fever, diminished cough, reduced number of organisms on AFB smear) and evidence of adherence with therapy. DOT is the standard of care for all TB patients in Georgia.

Patients must cover all coughs or sneezes with double tissues and dispose of the tissues directly into the toilet or into a paper or plastic bag before putting them in the trash.

All high risk contacts (i.e. immunocompromised individuals, inmates of correctional facilities, residents of long term care facilities, IVDUs, close contacts, children < 5 years of age) should be placed on treatment for latent TB infection for three months, unless otherwise contraindicated, regardless of results of skin testing (or IGRA test) and in the presence of a normal chest x-ray (if abnormal patient should be evaluated for active TB disease). If initial TST (or IGRA) is negative, the test should be repeated in three months.

NOTE: If patient is high risk for MDR-TB, manage as drug-resistant until susceptibility results are available and isolate is known to be drug susceptible. If at low risk for MDR-TB and clinically improving, patient can be managed with restrictions as for drug susceptible disease.

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IX. District Health Directors (by district)

Wade Sellers, M.D., MPH
Northwest Georgia Health District (Rome)
District 1, Unit 1
1309 Redmond Road, NW
Rome, GA 30165-9655
T: 706-295-6704
F: 706-802-5435
cwsellers@dhr.state.ga.us
AA: Kathy Kitchens
T: 706-295-6704

David N. Westfall, M.D., CPE
North Health District (Gainesville)
District 2
1280 Athens St
Gainesville GA 30507-7000
T: 770-535-5743
F: 770-535-5958
dnwestfall@dhr.state.ga.us
AA: Kathy Moreland
T: 770-535-5866

Harold W. Pitts, M.D., J.D.
North Georgia Health District (Dalton)
District 1, Unit 2
100 W Walnut Ave, Suite 92
Dalton GA 30720-8427
T: 706-272-2392
F: 706-272-2221
hwpitts@dhr.state.ga.us
AA: Jennifer Smith
T: 706-272-2342

John (Jack) Kennedy MD, MBA
Cobb/Douglas Health District
District 3, Unit 1
1650 County Services Pkwy
Marietta GA 30008-4010
T: 770-514-2330
F: 770-514-2320
JDKennedy@dhr.state.ga.us
AA: Virginia Freeman
T: 770-514-2330

Patrice Harris, M.D.
Fulton Health District
District 3, Unit 2
99 Jesse Hill Jr Dr SE
Atlanta GA 30303-3045
T: 404-730-1205
F: 404-730-1294
patrice.harris@fultoncountyga.gov
AA: Glenda Robinson
T : 404-730-1242

Alpha F. Bryan, M.D.
Clayton County Health District (Clayton)
District 3, Unit 3
1117 Battlecreek Rd
Jonesboro GA 30236-2407
T: 678-610-7199
F: 770-603-4872
afbryan@dhr.state.ga.us
AA: Helen Garrett
T: 678-610-7258

Lloyd M. Hofer, M.D., MPH
East Metro Health District (Gwinnett)
District 3, Unit 4
PO Box 897, 2570 Riverside Pkwy
Lawrenceville GA 30046-0897
T: 770-339-4260
F: 770-339-2334
lmhofer@dhr.state.ga.us
AA: Suzette Gonzales
T: 678-442-6908

S. Elizabeth Ford, MD, MBA
DeKalb Health District
District 3, Unit 5
PO Box 987
Decatur GA 30031-0987
T: 404-294-3787
F: 404-294-3715
seford@dhr.state.ga.us
AA: Sandra Piñeyro
T : 404-294-3787

G. Nicole Haynes, M.D., MPH
LaGrange Health District
District 4
122 Gordon Commercial Dr, Suite A
LaGrange GA 30240-5740
T: 706-845-4035
F: 706-845-4350
gnhaynes@dhr.state.ga.us
AA: Debbi Heard
T:706-845-4035 x219

David N. Harvey, M.D.
North Central Health District (Macon)
District 5, Unit 2
811 Hemlock St
Macon GA 31201-2198
T: 478-751-6247
F: 478-751-6099
dnharvey@dhr.state.ga.us
AA: 478-751-6247

Lawton C. Davis, M.D.
South Central Health District (Dublin)
District 5, Unit 1
2121-B Bellevue Rd
Dublin GA 31021-2998
T: 478-275-6545
F: 478-275-6575
lcdavis@dhr.state.ga.us
AA: Kay Stevenson
T: 478-275-6565

Ketty M. Gonzalez, M.D., M.S.
East Central Health District (Augusta)
District 6
1916 N Leg Rd
Augusta GA 30909-4437
T: 706-667-4250
F: 706-667-4365
kmgonzalez@dhr.state.ga.us
AA: Helen Smith
T: 706-667-4257

Beverley A. Townsend, M.D., MBA
West Central Health District (Columbus)
District 7
PO Box 2299
Columbus GA 31902-2299
T: 706-321-6300
F: 706-321-6126
batownsend@dhr.state.ga.us
AA: Carol Popwell
T : 706-321-6108

Jacqueline H. Grant, M.D., MPA, MPH
Southwest Health District (Albany)
District 8, Unit 2
1109 N. Jackson St
Albany GA 31701-2022
T: 229-430-4127
F: 229-430-5143
jhgrant@dhr.state.ga.us
AA: Nancy Rumph
T: 229-430-4127

William R. Grow, M.D., FACP
South Health District (Valdosta)
District 8, Unit 1
PO Box 5147
Valdosta GA 31603-5147
T: 229-333-5290
F: 229-333-7822
wrgrow@dhr.state.ga.us
AA: Theresa Clark
T: 229-245-6431

Diane Z. Weems, M.D. (Interim)
Coastal Health District (Savannah/Brunswick)
District 9, Unit 1
1395 Eisenhower Drive
Savannah GA 31406
T: 912-356-2897
C : 912-657-4629
F: 912-356-2868
dzweems@dhr.state.ga.us
AA: Ruthie Smoak
T : 912-644-5205

Rosemarie D. Parks, M.D., MPH
Southeast Health District (Waycross)
District 9, Unit 2
1101 Church St
Waycross GA 31501-3525
T: 912-285-6010
F: 912-284-2980
rdparks@dhr.state.ga.us
AA: Melinda Monroe
T : 912-285-6020

Claude A. Burnett, M.D., MPH
Northeast Health District (Athens)
District 10
220 Research Dr
Athens GA 30605-2738
T: 706-583-2870
F: 706-548-5181
cabmd@dhr.state.ga.us
AA: Linda McGinnis
T : 706-583-2870

Georgia Department of Public Health
Division of Health Protection
2 Peachtree Street, N.W.,
Atlanta, Georgia 30303
404-657-2634